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(54) Title: INHIBITORS OF FACTOR Xa

(57) Abstract: The present application relates to compounds of the general formula A-Y-D-E-G-J-Z-L, wherein A, Y, D, E, G, J, Z and L have the meanings given in the description, having activity against mammalian factor Xa. The compounds are useful *in vitro* or *in vivo* for preventing or treating coagulation disorders.

INHIBITORS OF FACTOR Xa

Related Applications

This application claims benefit of priority under 35 USC § 119(e) to U.S. Provisional Application No. 60/135,819 filed on May 24, 1999, which is herein incorporated in its entirety by reference.

Field of the Invention

This invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa or when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation (e.g. thrombin, fVIIa, fIXa) or the fibrinolytic cascades (e.g. plasminogen activators, plasmin). In another aspect, the present invention relates to novel monoamidino-containing compounds, their pharmaceutically acceptable salts, and pharmaceutically acceptable compositions thereof which are useful as potent and specific inhibitors of blood coagulation in mammals. In yet another aspect, the invention relates to methods for using these inhibitors as therapeutic agents for disease states in mammals characterized by coagulation disorders.

Background of the Invention

Hemostasis, the control of bleeding, occurs by surgical means, or by the physiological properties of vasoconstriction and coagulation. This invention is particularly concerned with blood coagulation and ways in which it assists in maintaining the integrity of mammalian circulation after injury, inflammation, disease, congenital defect, dysfunction or other disruption. Although platelets and blood coagulation are both involved in thrombus formation, certain components of the coagulation cascade are primarily responsible for the amplification or acceleration of the processes involved in platelet aggregation and fibrin deposition.

Thrombin is a key enzyme in the coagulation cascade as well as in hemostasis. Thrombin plays a central role in thrombosis through its ability to catalyze the conversion of fibrinogen into fibrin and through its potent platelet activation activity. Direct or indirect inhibition of thrombin activity has been the focus of a variety of recent anticoagulant strategies as reviewed by Claeson, G.,

"Synthetic Peptides and Peptidomimetics as Substrates and Inhibitors of Thrombin and Other Proteases in the Blood Coagulation System", Blood Coag. Fibrinol. 5, 411-436 (1994). Several classes of anticoagulants currently used in the clinic directly or indirectly affect thrombin (i.e. heparins, low-molecular weight heparins, heparin-like compounds and coumarins).

A prothrombinase complex, including Factor Xa (a serine protease, the activated form of its Factor X precursor and a member of the calcium ion binding, gamma carboxyglutamyl (Gla)-containing, vitamin K dependent, blood coagulation glycoprotein family), converts the zymogen prothrombin into the active procoagulant thrombin. Unlike thrombin, which acts on a variety of protein substrates as well as at a specific receptor, factor Xa appears to have a single physiologic substrate, namely prothrombin. Since one molecule of factor Xa may be able to generate up to 138 molecules of thrombin (Elodi et al., *Thromb. Res.* 15, 617-619 (1979)), direct inhibition of factor Xa as a way of indirectly inhibiting the formation of thrombin may be an efficient anticoagulant strategy. Therefore, it has been suggested that compounds which selectively inhibit factor Xa may be useful as *in vitro* diagnostic agents, or for therapeutic administration in certain thrombotic disorders, see *e.g.*, WO 94/13693.

Polypeptides derived from hematophagous organisms have been reported which are highly potent and specific inhibitors of factor Xa. United States Patent 4,588,587 describes anticoagulant activity in the saliva of the Mexican leech, *Haementeria officinalis*. A principal component of this saliva was shown to be the polypeptide factor Xa inhibitor, antistasin (ATS), by Nutt, E. *et al.*, "The Amino Acid Sequence of Antistasin, a Potent Inhibitor of Factor Xa Reveals a Repeated Internal Structure", J. Biol. Chem., 263, 10162-10167 (1988). Another potent and highly specific inhibitor of Factor Xa, called tick anticoagulant peptide (TAP), has been isolated from the whole body extract of the soft tick *Ornithidoros moubata*, as reported by Waxman, L., *et al.*, "Tick Anticoagulant Peptide (TAP) is a Novel Inhibitor of Blood Coagulation Factor Xa" Science, 248, 593-596 (1990).

Factor Xa inhibitory compounds which are not large polypeptide-type inhibitors have also been reported including: Tidwell, R.R. *et al.*, "Strategies for Anticoagulation With Synthetic Protease Inhibitors. Xa Inhibitors Versus Thrombin Inhibitors", Thromb. Res., 19, 339-349 (1980); Turner, A.D. *et al.*, "p-Amidino Esters as Irreversible Inhibitors of Factor IXa and Xa and Thrombin", Biochemistry,

25, 4929-4935 (1986); Hitomi, Y. *et al.*, "Inhibitory Effect of New Synthetic Protease Inhibitor (FUT-175) on the Coagulation System", Haemostasis, 15, 164-168 (1985); Sturzebecher, J. *et al.*, "Synthetic Inhibitors of Bovine Factor Xa and Thrombin. Comparison of Their Anticoagulant Efficiency", Thromb. Res., 54, 245-252 (1989); Kam, C.M. *et al.*, "Mechanism Based Isocoumarin Inhibitors for Trypsin and Blood Coagulation Serine Proteases: New Anticoagulants", Biochemistry, 27, 2547-2557 (1988); Hauptmann, J. *et al.*, *"Comparison* of the Anticoagulant and Antithrombotic Effects of Synthetic Thrombin and Factor Xa Inhibitors", Thromb. Haemost., 63, 220-223 (1990); and the like.

Others have reported Factor Xa inhibitors which are small molecule organic compounds, such as nitrogen containing heterocyclic compounds which have amidino substituent groups, wherein two functional groups of the compounds can bind to Factor Xa at two of its active sites. For example, WO 98/28269 describes pyrazole compounds having a terminal C(=NH)-NH_2 group; WO 97/21437 describes benzimidazole compounds substituted by a basic radical which are connected to a naththyl group via a straight or branched chain alkylene,-C(=O) or -$S(=O)_2$ bridging group; WO 99/10316 describes compounds having a 4-phenyl-N-alkylamidino-piperidine and 4-phenoxy-N-alkylamidino-piperidine group connected to a 3-amidinophenyl group via a carboxamidealkyleneamino bridge; and EP 798295 describes compounds having a 4-phenoxy-N-alkylamidino-piperidine group connected to an amidinonaphthyl group via a substituted or unsubstituted sulfonamide or carboxamide bridging group.

There exists a need for effective therapeutic agents for the regulation of hemostasis, and for the prevention and treatment of thrombus formation and other pathological processes in the vasculature induced by thrombin such as restenosis and inflammation. In particular, there continues to be a need for compounds which selectively inhibit factor Xa or its precursors. Compounds that have different combinations of bridging groups and functional groups than compounds previously discovered are needed, particularly compounds which selectively or preferentially bind to Factor Xa. Compounds with a higher degree of binding to Factor Xa than to thrombin are desired, especially those compounds having good bioavailability and/or solubility.

Summary of the Invention

The present invention relates to novel compounds which inhibit factor Xa, their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives, and pharmaceutically acceptable compositions thereof which have particular biological properties and are useful as potent and specific inhibitors of blood coagulation in mammals. In another aspect, the invention relates to methods of using these inhibitors as diagnostic reagents or as therapeutic agents for disease states in mammals which have coagulation disorders, such as in the treatment or prevention of any thrombotically mediated acute coronary or cerebrovascular syndrome, any thrombotic syndrome occurring in the venous system, any coagulopathy, and any thrombotic complications associated with extracorporeal circulation or instrumentation, and for the inhibition of coagulation in biological samples.

In certain embodiments, this invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation cascade (e.g. thrombin, etc.) or the fibrinolytic cascade, and are useful as diagnostic reagents as well as antithrombotic agents.

In a preferred embodiment, the present invention provides a compound of the formula I:

A-Y-D-E-G-J-Z-L

wherein:

A is selected from:

(a) phenyl, which is independently substituted with 0-2 R^1 substituents;

(b) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^1 substituents;

(c) naphthyl, which is independently substituted with 0-2 R^1 substituents;

(d) C_1-C_6-alkyl; C_3-C_8-cycloalkyl; and

(e) $-NR^2R^3$, $-C(=NR^2)NR^2R^3$, $-NR^2C(=NR^2)NR^2R^3$, $-C(=NR^2)R^4$, and $NR^2C(=NR^2)$-R^3

R^1 is selected from:

Halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl,-CN, $-NO_2$, $-(CH_2)_mNR^2R^3$, $-C(=O)NR^2R^3$, $-C(=NR^2)NR^2R^3$, $-NR^2C(=NR^2)NR^2R^3$, $-C(=NR^2)R^4$ and $NR^2C(=NR^2)$-R^3, $-SO_2NR^2R^3$, $-SO_2R^2$, $-CF_3$, $-OR^2$, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl and $-NO_2$;

R^2 and R^3 are independently selected from the group consisting of:

H, $-OR^{14}$, $-NR^{14}R^{15}$, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, $COOC_{1-4}$alkyl, COO-C_{0-4}alkylphenyl C_{0-4}alkylphenyl and C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and $-NO_2$;

m is an integer of 0-2;

Y is a member selected from the group consisting of:

a direct link, $-C(=O)-$, $-N(R^4)-$, $-C(=O)-N(R^4)-$, $-N(R^4)-C(=O)-$, $-SO_2-$, -O-, $-SO_2-N(R^4)-$, $-N(R^4)-SO_2-$, $-C(=NR^4)$, $-C(=S)-$, $-CH_2-$, $-CH_2N(R^4)-$;

R^4 is selected from:

H, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, C_{0-4}alkylphenyl and C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl,

C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and $-NO_2$;.

D is a direct link or is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0-2 R^{1a} substituents;

(b) naphthyl, which is independently substituted with 0-2 R^{1a} substituents; and

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1a} substituents;

R^{1a} is selected from:

Halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, $-NO_2$, $(CH_2)_mNR^{2a}R^{3a}$, $SO_2NR^{2a}R^{3a}$, SO_2R^{2a}, CF_3, OR^{2a}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN and $-NO_2$;

m is an integer of 0-2;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, C_{0-4}alkylphenyl and C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN and $-NO_2$;.

E is a member selected from the group consisting of:

$-N(R^5)-C(=O)-$, $-C(=O)-N(R^5)-$, $-N(R^5)-C(=O)-N(R^6)-$, $-SO_2-N(R^5)-$, $-N(R^5)-SO_2-N(R^6)-$ and $-N(R^5)-SO_2-N(R^6)-C(=O)-$;

R^5 and R^6 are independently selected from:

H, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, C_{0-4}alkylphenyl, C_{0-4}alkylnaphthyl, C_{0-4}alkylheteroaryl, C_{1-4}alkylCOOH and C_{1-4}alkylCOOC_{1-4}alkyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl, naphthyl and heteroaryl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN and $-NO_2$;

G is selected from:

$-CR^7R^8-$ and $-CR^{7a}R^{8a}-C^bR^{8b}-$

Wherein R^7, R^8, R^{7a}, R^{8a}, R^{7b} and R^{8b} are each independently a member selected from the group consisting of:

hydrogen, halo, $-C_{1-6}$alkyl, haloalkyl, -CN, $-NO_2$, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkyl-C_{3-8}-cycloalkyl, $-C_{0-4}$alkyl-CN, $-C_{0-4}$alkyl-NO_2, $-C_{0-4}$alkyl-O-R^9, $-C_{0-4}$alkyl-S-R^9, $-C_{0-4}$alkyl-$S(=O)_2$-R^9, $-C_{0-4}$alkyl-S(O)-R^9, $-C_{0-4}$alkyl-C(=O)-OR^9, $-C_{0-4}$alkyl-C(=O)-N(R^{9a}, R^{9b}), $-C_{0-4}$alkyl-C(=O)-R^9, $-C_{0-4}$alkyl-N(R^{9a}, R^{9b}), $-C_{0-4}$alkyl-N(-R^{9a})-C(=O)-R^{9b}), $-C_{0-4}$alkyl-N(-R^{9a})-C(=O)-R^{9b}, $-C_{0-4}$alkyl-N(-R^{9a})-C(=O)-N(-R^{9b}), $-C_{0-4}$alkyl-N(-R^{9a})-$S(=O)_2$-R^{9b}, $-C_{0-4}$alkyl-$S(=O)_2$-N(R^{9a}, R^{9b}), $-C_{0-4}$alkyl-$S(=O)_2$-R^9, $-C_{0-4}$alkyl-P(=O)(-OR^{9a})(-OR^{9b}), $-C_{0-4}$alkyl-N(-R^9)-P(=O)(-OR^{9a})(-OR^{9b}), $-C_{0-4}$alkyl-phenyl, $-C_{0-4}$alkyl-naphthyl, $-C_{0-4}$alkyl-heterocyclic ring system containing from 1-4 heteroatoms selected from the group consisting of O, N and S, wherein the heterocyclic ring system is a 5-6 membered monocyclic ring or a 8-12 membered bicyclic ring, and wherein 0-4 hydrogen atoms of the phenyl ring, the naphthyl ring carbon and the heterocyclic ring system are replaced by a member selected from the group consisting of $-C_{1-4}$alkyl, haloalkyl, halo, -CN, $-NO_2$, -OR^{9c}, -SR^{9c}, -S(O)R^{9c}, -C(=O)-OR^{9c}, -C(=O)-N(-R^{9c}, R^{9d}), -C(=O)-R^{9c}, -N(R^{9c}, R^{9d}),

-N(-R^{9c})-C(=O)-R^{9d}, -N(-R^{9c})-C(=O)-OR^{9d}, -N(-R^{9c})-C(=O)-N(-H, R^{9d}), -N(-R^{9c})-SO_2-R^{9d}, -SO_2-N(-R^{9c}, -R^{9d}), -SO_2-R^{9c}; or one of R^7, R^8, R^{7a}, R^{8a}, R^{7b} and R^{8b} can combine with a nitrogen on the E group to form a 5-7 membered heterocyclic ring containing a 0-3 additional heteroatoms selected from the group consisting of O, N and S; or R^{7a} and R^{7b} on adjacent carbons combine to form a 3-6 membered carbocyclic ring;

R^{7b} and R^{8b} combine to form alkylidene groups, such as H_2C=, C_{1-4}alkylCH=, $(C_{1-4}alkyl)_2C$=, PhCH=;

R^9, R^{9a}, R^{9b}, R^{9c} and R^{9d} are each independently a member selected from the group consisting of:

H, halo -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkyl-C_{3-8}cycloalkyl, -CH_2CH_2OH, -CH_2CH_2-O-CH_3, -C_{0-4}alkylphenyl, -C_{0-4}alkylheterocycle wherein the heterocycle may be a 5-6 membered ring, and wherein from 0-4 hydrogen atoms from the ring atoms of the phenyl and heterocycle groups may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkyl-C_{3-8}cycloalkyl, -CN, -NO_2, -C(=O)-OH, -C(=O)-O-C_{1-4}alkyl, -C(=O)-NH_2, -C(=O)-N(-H, -C1-4alkyl), and -C(=O)-N(-C_{1-4}alkyl, -C_{1-4}alkyl);

alternatively, R^{9a} taken with R^{9b} or R^{9c} taken with R^{9d} when either pair of groups is attached to the same nitrogen atom may combine with that nitrogen atom to form a 5-8 membered saturated, partially saturated or unsaturated ring which contains from 0-1 additional heteroatoms selected from a group consisting of -N, -O, S, wherein any S ring atom may be present as a -S-, -S(=O)- or -$S(=O)_2$- group;

J is a member selected from the group consisting of:

a direct link, -CH(R^{11})- and -CH(R^{11})-CH_2-;

R^{11} is a member selected from the group consisting of:

hydrogen, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkyl-C_{3-8}cycloalkyl, C_{0-4}alkylphenyl, C_{0-4}alkylnaphthyl, C_{0-4}alkylheterocyclic ring

having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S, CH_2COOC_{1-4}alkyl, CH_2COOC_{1-4}alkylphenyl and CH_2COOC_{1-4}alkylnaphthyl;

Z is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0-2 R^{1b} substituents;

(b) naphthyl, which is independently substituted with 0-2 R^{1b} substituents; and

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1b} substituents;

R^{1b} is selected from:

Halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, $-NO_2$, $NR^{2b}R^{3b}$, $SO_2NR^{2b}R^{3b}$, SO_2R^{2b}, CF_3, OR^{2b}, O-CH_2-CH_2-OR^{2b}, O-CH_2-$COOR^{2b}$, N(R^{2b})-CH_2-CH_2-OR^{2b}, N(-CH_2-CH_2-OR^{2b})$_2$, N(R^{2b})-C(=O)R^{3b}, N(R^{2b})-SO_2-R^{3b}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN and $-NO_2$;

R^{2b} and R^{3b} are independently selected from the group consisting of:

H, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, C_{0-4}alkylphenyl and C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN and $-NO_2$;

L is selected from:

H, -CN, $C(=O)NR^{12}R^{13}$, $(CH_2)_nNR^{12}R^{13}$, $C(=NR^{12})NR^{12}R^{13}$, $NR^{12}R^{13}$, OR^{12}, $-NR^{12}C(=NR^{12})NR^{12}R^{13}$, and $NR^{12}C(=NR^{12})-R^{13}$;

n is an integer of 0-2;

R^{12} and R^{13} are independently selected from:

hydrogen, $-OR^{14}$, $-NR^{14}R^{15}$, C_{1-4}alkyl, C_{0-4}alkylphenyl, C_{0-4}alkylnaphthyl, $COOC_{1-4}$alkyl, $COO\text{-}C_{0-4}$alkylphenyl and $COO\text{-}C_{0-4}$alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and $-NO_2$;

R^{14} and R^{15} are independently selected from:

H, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, C_{0-4}alkylphenyl and C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and $-NO_2$;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In certain aspects of this invention, compounds are provided which are useful as diagnostic reagents. In another aspect, the present invention includes pharmaceutical compositions comprising a pharmaceutically effective amount of the compounds of this invention and a pharmaceutically acceptable carrier. In yet another aspect, the present invention includes methods comprising using the above compounds and pharmaceutical compositions for preventing or treating disease states characterized by undesired thrombosis or disorders of the blood coagulation process in mammals, or for preventing coagulation in biological samples such as, for example, stored blood products and samples. Optionally, the methods of this invention comprise administering the pharmaceutical composition in combination with an additional therapeutic agent such as an antithrombotic and/or a thrombolytic agent and/or an anticoagulant.

The preferred compounds also include their pharmaceutically acceptable isomers, hydrates, solvates, salts and prodrug derivatives.

Detailed Description of the Invention

Definitions

In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "alkenyl" refers to a trivalent straight chain or branched chain unsaturated aliphatic radical. The term "alkinyl" (or "alkynyl") refers to a straight or branched chain aliphatic radical that includes at least two carbons joined by a triple bond. If no number of carbons is specified alkenyl and alkinyl each refer to radicals having from 2-12 carbon atoms.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain and cyclic groups having the number of carbon atoms specified, or if no number is specified, having up to 12 carbon atoms. The term "cycloalkyl" as used herein refers to a mono-, bi-, or tricyclic aliphatic ring having 3 to 14 carbon atoms and preferably 3 to 7 carbon atoms.

As used herein, the terms "carbocyclic ring structure " and " C_{3-16} carbocyclic mono, bicyclic or tricyclic ring structure" or the like are each intended to mean stable ring structures having only carbon atoms as ring atoms wherein the ring structure is a substituted or unsubstituted member selected from the group consisting of: a stable monocyclic ring which is aromatic ring ("aryl") having six ring atoms; a stable monocyclic non-aromatic ring having from 3 to 7 ring atoms in the ring; a stable bicyclic ring structure having a total of from 7 to 12 ring atoms in the two rings wherein the bicyclic ring structure is selected from the group consisting of ring structures in which both of the rings are aromatic, ring structures in which one of the rings is aromatic and ring structures in which both of the rings are non-aromatic; and a stable tricyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein the tricyclic ring structure is selected from the group consisting of: ring structures in which three of the rings are aromatic, ring structures in which two of the rings are aromatic and ring structures in which three of the rings are non-aromatic. In each case, the non-aromatic rings when present in the monocyclic, bicyclic or tricyclic ring structure may independently be saturated, partially saturated

or fully saturated. Examples of such carbocyclic ring structures include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), 2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin). Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any carbon atom which results in a stable structure. The term "substituted" as used in conjunction with carbocyclic ring structures means that hydrogen atoms attached to the ring carbon atoms of ring structures described herein may be substituted by one or more of the substituents indicated for that structure if such substitution(s) would result in a stable compound.

The term "aryl" which is included with the term "carbocyclic ring structure" refers to an unsubstituted or substituted aromatic ring, substituted with one, two or three substituents selected from loweralkoxy, loweralkyl, loweralkylamino, hydroxy, halogen, cyano, hydroxyl, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl, carboalkoxy and carboxamide, including but not limited to carbocyclic aryl, heterocyclic aryl, and biaryl groups and the like, all of which may be optionally substituted. Preferred aryl groups include phenyl, halophenyl, loweralkylphenyl, napthyl, biphenyl, phenanthrenyl and naphthacenyl.

The term "arylalkyl" which is included with the term "carbocyclic aryl" refers to one, two, or three aryl groups having the number of carbon atoms designated, appended to an alkyl group having the number of carbon atoms designated. Suitable arylalkyl groups include, but are not limited to, benzyl, picolyl, naphthylmethyl, phenethyl, benzyhydryl, trityl, and the like, all of which may be optionally substituted.

As used herein, the term "heterocyclic ring" or "heterocyclic ring system" is intended to mean a substituted or unsubstituted member selected from the group consisting of stable monocyclic ring having from 5-7 members in the ring itself and having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S; a stable bicyclic ring structure having a total of from 7 to 12 atoms in the two rings wherein at least one of the two rings has from 1 to 4 hetero atoms selected from N, O and S, including bicyclic ring structures wherein any of the described stable monocyclic heterocyclic rings is fused to a hexane or benzene ring; and a stable tricyclic heterocyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein at least one of the three rings has from 1 to 4 hetero atoms

selected from the group consisting of N, O and S. Any nitrogen and sulfur atoms present in a heterocyclic ring of such a heterocyclic ring structure may be oxidized. Unless indicated otherwise the terms "heterocyclic ring" or "heterocyclic ring system" include aromatic rings, as well as non-aromatic rings which can be saturated, partially saturated or fully saturated non-aromatic rings. Also, unless indicated otherwise the term "heterocyclic ring system" includes ring structures wherein all of the rings contain at least one hetero atom as well as structures having less than all of the rings in the ring structure containing at least one hetero atom, for example bicyclic ring structures wherein one ring is a benzene ring and one of the rings has one or more hetero atoms are included within the term "heterocyclic ring systems" as well as bicyclic ring structures wherein each of the two rings has at least one hetero atom. Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any hetero atom or carbon atom which results in a stable structure. Further, the term "substituted" means that one or more of the hydrogen atoms on the ring carbon atom(s) or nitrogen atom(s) of the each of the rings in the ring structures described herein may be replaced by one or more of the indicated substituents if such replacement(s) would result in a stable compound. Nitrogen atoms in a ring structure may be quaternized, but such compounds are specifically indicated or are included within the term "a pharmaceutically acceptable salt" for a particular compound. When the total number of O and S atoms in a single heterocyclic ring is greater than 1, it is preferred that such atoms not be adjacent to one another. Preferably, there are no more that 1 O or S ring atoms in the same ring of a given heterocyclic ring structure.

Examples of monocylic and bicyclic heterocylic ring systems, in alphabetical order, are acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl,

phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pryidooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl. Preferred heterocyclic ring structures include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolinyl, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocylic ring structures.

As used herein the term "aromatic heterocyclic ring system" has essentially the same definition as for the monocyclic and bicyclic ring systems except that at least one ring of the ring system is an aromatic heterocyclic ring or the bicyclic ring has an aromatic or non-aromatic heterocyclic ring fused to an aromatic carbocyclic ring structure.

The terms "halo" or "halogen" as used herein refer to Cl, Br, F or I substituents. The term "haloalkyl", and the like, refer to an aliphatic carbon radicals having at least one hydrogen atom replaced by a Cl, Br, F or I atom, including mixtures of different halo atoms. Trihaloalkyl includes trifluoromethyl and the like as preferred radicals, for example.

The term "methylene" refers to $-CH_2-$.

The term "pharmaceutically acceptable salts" includes salts of compounds derived from the combination of a compound and an organic or inorganic acid. These compounds are useful in both free base and salt form. In practice, the use of the salt form amounts to use of the base form; both acid and base addition salts are within the scope of the present invention.

"Pharmaceutically acceptable acid addition salt" refers to salts retaining the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as

hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicyclic acid and the like.

"Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

"Biological property" for the purposes herein means an *in vivo* effector or antigenic function or activity that is directly or indirectly performed by a compound of this invention that are often shown by *in vitro* assays. Effector functions include receptor or ligand binding, any enzyme activity or enzyme modulatory activity, any carrier binding activity, any hormonal activity, any activity in promoting or inhibiting adhesion of cells to an extracellular matrix or cell surface molecules, or any structural role. Antigenic functions include possession of an epitope or antigenic site that is capable of reacting with antibodies raised against it.

In the compounds of this invention, carbon atoms bonded to four non-identical substituents are asymmetric. Accordingly, the compounds may exist as diastereoisomers, enantiomers or mixtures thereof. The syntheses described herein may employ racemates, enantiomers or diastereomers as starting materials or intermediates. Diastereomeric products resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods known in the art. Likewise, enantiomeric product mixtures may be separated using

the same techniques or by other methods known in the art. Each of the asymmetric carbon atoms, when present in the compounds of this invention, may be in one of two configurations (R or S) and both are within the scope of the present invention.

Preferred Embodiments

In a preferred embodiment, the present invention provides a compound of the formula I:

A-Y-D-E-G-J-Z-L

wherein:

A is selected from:

(a) phenyl, which is independently substituted with 0-2 R^1 substituents;

(b) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^1 substituents;

(c) naphthyl, which is independently substituted with 0-2 R^1 substituents;and

(d) C_1-C_6-alkyl; C_3-C_8-cycloalkyl;

(e) $-NR^2R^3$, $-C(=NR^2)NR^2R^3$, $-NR^2C(=NR^2)NR^2R^3$, $-C(=NR^2)R^4$, and $NR^2C(=NR^2)$-R^3

R^1 is selected from:

Halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl,-CN, $-NO_2$, $-(CH_2)_mNR^2R^3$, $-C(=O)NR^2R^3$, $-C(=NR^2)NR^2R^3$, $-NR^2C(=NR^2)NR^2R^3$, $-C(=NR^2)R^4$ and $NR^2C(=NR^2)$-R^3, $-SO_2NR^2R^3$, $-SO_2R^2$, $-CF_3$, $-OR^2$, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl and $-NO_2$;

R^2 and R^3 are independently selected from the group consisting of:

H, $-OR^{14}$, $-NR^{14}R^{15}$, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, $COOC_{1-4}$alkyl, COO-C_{0-4}alkylphenyl C_{0-4}alkylphenyl and C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and $-NO_2$;

m is an integer of 0-2;

Y is a member selected from the group consisting of:

a direct link, $-C(=O)-$, $-N(R^4)-$, $-C(=O)-N(R^4)-$, $-N(R^4)-C(=O)-$, $-SO_2-$, -O-, $-SO_2-N(R^4)-$, $-N(R^4)-SO_2-$, $-C(=NR^4)$, $-C(=S)-$, $-CH_2-$, $-CH_2N(R^4)-$;

R^4 is selected from:

H, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, C_{0-4}alkylphenyl and C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and $-NO_2$;.

D is a direct link or is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0-2 R^{1a} substituents;

(b) naphthyl, which is independently substituted with 0-2 R^{1a} substituents; and

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1a} substituents;

R^{1a} is selected from:

Halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, $-NO_2$, $(CH_2)_mNR^{2a}R^{3a}$, $SO_2NR^{2a}R^{3a}$, SO_2R^{2a}, CF_3, OR^{2a}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN and $-NO_2$;

m is an integer of 0-2;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, C_{0-4}alkylphenyl and C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN and $-NO_2$;.

E is a member selected from the group consisting of:

$-N(R^5)-C(=O)-$, $-C(=O)-N(R^5)-$, $-N(R^5)-C(=O)-N(R^6)-$, $-SO_2-N(R^5)-$, $-N(R^5)-SO_2-N(R^6)-$ and $-N(R^5)-SO_2-N(R^6)-C(=O)-$;

R^5 and R^6 are independently selected from:

H, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, C_{0-4}alkylphenyl, C_{0-4}alkylnaphthyl, C_{0-4}alkylheteroaryl, C_{1-4}alkylCOOH and C_{1-4}alkylCOOC_{1-4}alkyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl, naphthyl and heteroaryl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN and $-NO_2$;

G is selected from:

$-CR^7R^8-$ and $-CR^{7a}R^{8a}-C^bR^{8b}$

Wherein R^7, R^8, R^{7a}, R^{8a}, R^{7b} and R^{8b} are each independently a member selected from the group consisting of:

hydrogen, halo, -C_{1-6}alkyl, haloalkyl, -CN, -NO_2, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkyl-C_{3-8}-cycloalkyl, -C_{0-4}alkyl-CN, -C_{0-4}alkyl-NO_2, -C_{0-4}alkyl-O-R^9, -C_{0-4}alkyl-S-R^9, -C_{0-4}alkyl-$S(=O)_2$-R^9, -C_{0-4}alkyl-S(O)-R^9, -C_{0-4}alkyl-C(=O)-OR^9, -C_{0-4}alkyl-C(=O)-N(R^{9a}, R^{9b}), -C_{0-4}alkyl-C(=O)-R^9, -C_{0-4}alkyl-N(R^{9a}, R^{9b}), -C_{0-4}alkyl-N(-R^{9a})-C(=O)-R^{9b}), -C_{0-4}alkyl-N(-R^{9a})-C(=O)-R^{9b}, -C_{0-4}alkyl-N(-R^{9a})-C(=O)-N(-R^{9b}), -C_{0-4}alkyl-N(-R^{9a})-$S(=O)_2$-R^{9b}, -C_{0-4}alkyl-$S(=O)_2$-N(R^{9a}, R^{9b}), -C_{0-4}alkyl-$S(=O)_2$-R^9, -C_{0-4}alkyl-P(=O)(-OR^{9a})(-OR^{9b}), -C_{0-4}alkyl-N(-R^9)-P(=O)(-OR^{9a})(-OR^{9b}), -C_{0-4}alkyl-phenyl, -C_{0-4}alkyl-naphthyl, -C_{0-4}alkyl-heterocyclic ring system containing from 1-4 heteroatoms selected from the group consisting of O, N and S, wherein the heterocyclic ring system is a 5-6 membered monocyclic ring or a 8-12 membered bicyclic ring, and wherein 0-4 hydrogen atoms of the phenyl ring, the naphthyl ring carbon and the heterocyclic ring system are replaced by a member selected from the group consisting of -C_{1-4}alkyl, haloalkyl, halo, -CN, -NO_2, -OR^{9c}, -SR^{9c}, -S(O)R^{9c}, -C(=O)-OR^{9c}, -C(=O)-N(-R^{9c}, R^{9d}), -C(=O)-R^{9c}, -N(R^{9c}, R^{9d}), -N(-R^{9c})-C(=O)-R^{9d}, -N(-R^{9c})-C(=O)-OR^{9d}, -N(-R^{9c})-C(=O)-N(-H, R^{9d}), -N(-R^{9c})-SO_2-R^{9d}, -SO_2-N(-R^{9c}, -R^{9d}), -SO_2-R^{9c}; or one of R^7, R^8, R^{7a}, R^{8a}, R^{7b} and R^{8b} can combine with a nitrogen on the E group to form a 5-7 membered heterocyclic ring containing a 0-3 additional heteroatoms selected from the group consisting of O, N and S; or R^{7a} and R^{7b} on adjacent carbons combine to form a 3-6 membered carbocyclic ring;

R^{7b} and R^{8b} combine to form alkylidene groups, such as H_2C=, C_{1-4}alkylCH=, $(C_{1-4}alkyl)_2C$=, PhCH=;

R^9, R^{9a}, R^{9b}, R^{9c} and R^{9d} are each independently a member selected from the group consisting of:

H, halo -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkyl-C_{3-8}cycloalkyl, -CH_2CH_2OH, -CH_2CH_2-O-CH_3, -C_{0-4}alkylphenyl, -C_{0-4}alkylheterocycle wherein the heterocycle may be a 5-6 membered ring, and wherein from 0-4 hydrogen atoms from the ring atoms of the phenyl and

heterocycle groups may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkyl-C_{3-8}cycloalkyl, -CN, -NO_2, -C(=O)-OH, -C(=O)-O-C_{1-4}alkyl, -C(=O)-NH_2, -C(=O)-N(-H, -C1-4alkyl), and -C(=O)-N(-C_{1-4}alkyl, -C_{1-4}alkyl);

alternatively, R^{9a} taken with R^{9b} or R^{9c} taken with R^{9d} when either pair of groups is attached to the same nitrogen atom may combine with that nitrogen atom to form a 5-8 membered saturated, partially saturated or unsaturated ring which contains from 0-1 additional heteroatoms selected from a group consisting of -N, -O, S, wherein any S ring atom may be present as a -S-, -S(=O)- or -$S(=O)_2$- group;

J is a member selected from the group consisting of:

a direct link, -CH(R^{11})- and -CH(R^{11})-CH_2-;

R^{11} is a member selected from the group consisting of:

hydrogen, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkyl-C_{3-8}cycloalkyl, C_{0-4}alkylphenyl, C_{0-4}alkylnaphthyl, C_{0-4}alkylheterocyclic ring having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S, CH_2COOC_{1-4}alkyl, CH_2COOC_{1-4}alkylphenyl and CH_2COOC_{1-4}alkylnaphthyl;

Z is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0-2 R^{1b} substituents;

(b) naphthyl, which is independently substituted with 0-2 R^{1b} substituents; and

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1b} substituents;

R^{1b} is selected from:

Halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, $-NO_2$, $NR^{2b}R^{3b}$, $SO_2NR^{2b}R^{3b}$, SO_2R^{2b}, CF_3, OR^{2b}, O-CH_2-CH_2-OR^{2b}, O-CH_2-$COOR^{2b}$, N(R^{2b})-CH_2-CH_2-OR^{2b}, N(-CH_2-CH_2-OR^{2b})$_2$, N(R^{2b})-C(=O)R^{3b}, N(R^{2b})-SO_2-R^{3b}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN and $-NO_2$;

R^{2b} and R^{3b} are independently selected from the group consisting of:

H, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, C_{0-4}alkylphenyl and C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN and $-NO_2$;

L is selected from:

H, -CN, C(=O)$NR^{12}R^{13}$, $(CH_2)_nNR^{12}R^{13}$, C(=NR^{12})$NR^{12}R^{13}$, $NR^{12}R^{13}$, $NR^{12}R^{13}$, OR^{12}, -NR^{12}C(=NR^{12})$NR^{12}R^{13}$, and NR^{12}C(=NR^{12})-R^{13};

n is an integer of 0-2;

R^{12} and R^{13} are independently selected from:

hydrogen, -OR^{14}, -$NR^{14}R^{15}$, C_{1-4}alkyl, C_{0-4}alkylphenyl, C_{0-4}alkylnaphthyl, $COOC_{1-4}$alkyl, COO-C_{0-4}alkylphenyl and COO-C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and $-NO_2$;

R^{14} and R^{15} are independently selected from:

H, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, C_{0-4}alkylphenyl and C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on

the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and $-NO_2$;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In certain aspects of this invention, compounds are provided which are useful as diagnostic reagents. In another aspect, the present invention includes pharmaceutical compositions comprising a pharmaceutically effective amount of the compounds of this invention and a pharmaceutically acceptable carrier. In yet another aspect, the present invention includes methods comprising using the above compounds and pharmaceutical compositions for preventing or treating disease states characterized by disorders of the blood coagulation process in mammals, or for preventing coagulation in stored blood products and samples. Optionally, the methods of this invention comprise administering the pharmaceutical composition in combination with an additional therapeutic agent such as an antithrombotic and/or a thrombolytic agent and/or an anticoagulant.

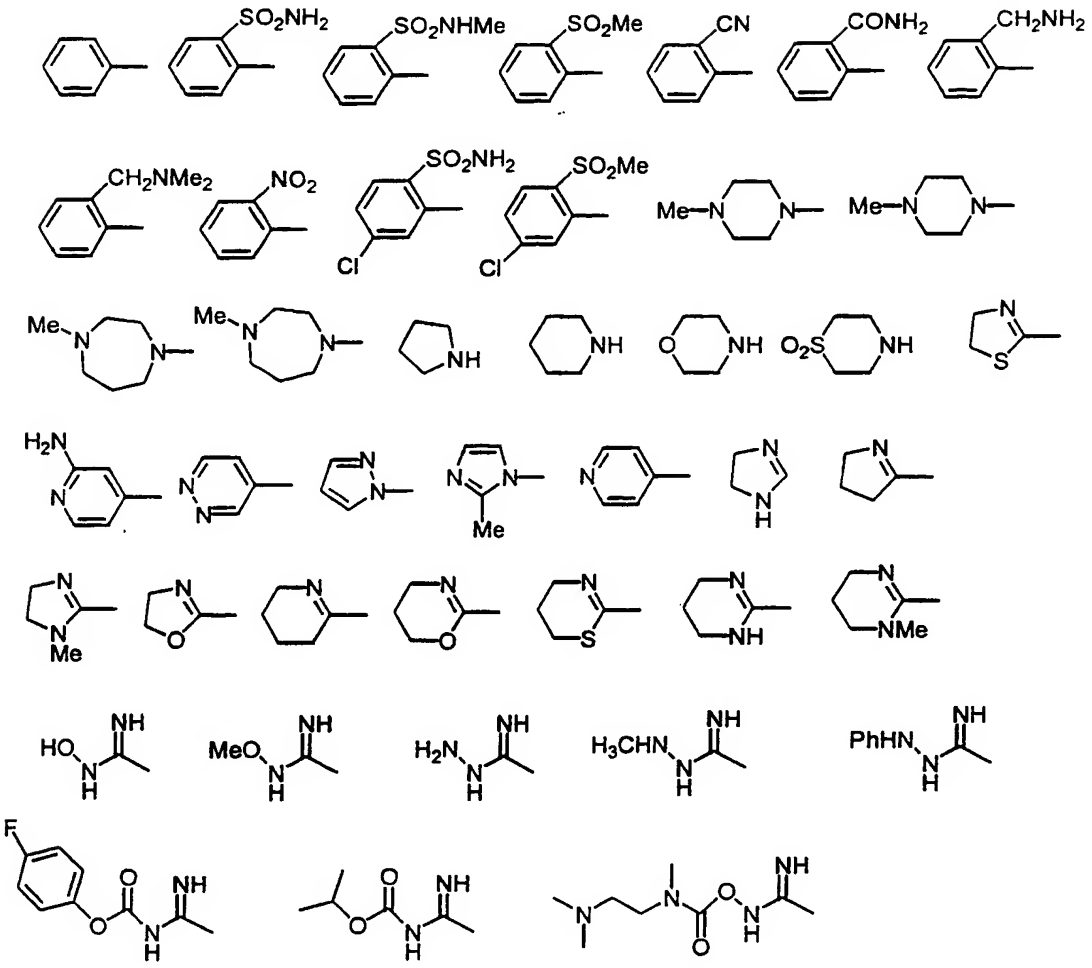
The preferred compounds also include their pharmaceutically acceptable isomers, hydrates, solvates, salts and prodrug derivatives.

In a further preferred embodiment, the present invention provides a compound according to the formula I:

A-Y-D-E-G-J-Z-L

wherein:

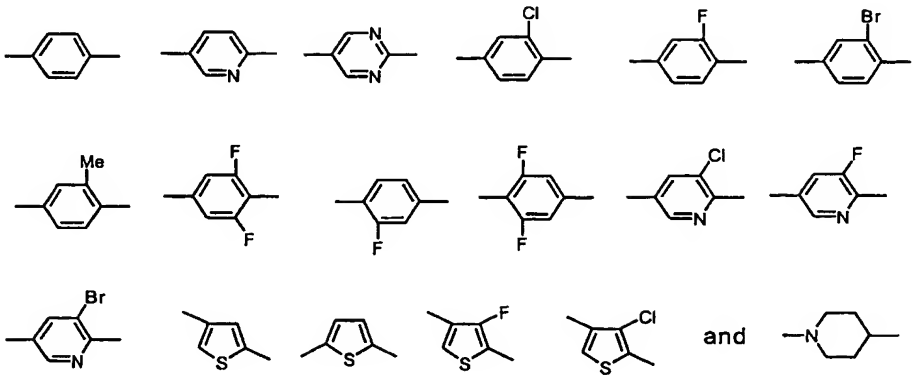
A is a member selected from the group consisting of:



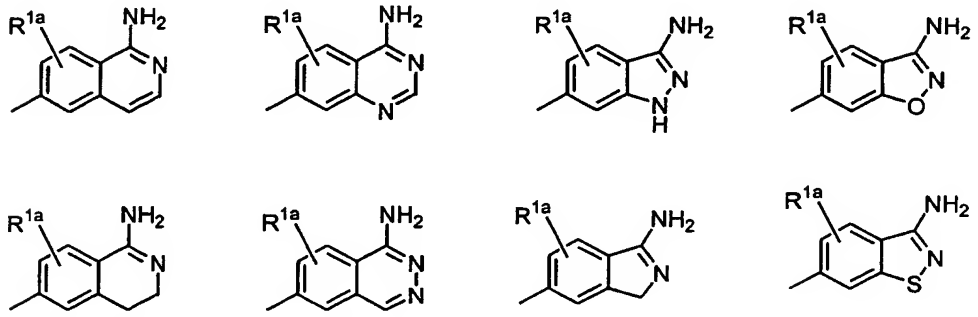
Y is a member selected from the group consisting of:

a direct link, -C(=O)-; -N(-CH_3)-; -N(CH_3)-CH_2-; -C(=NH)-, -CH_2-, –C(=S)-, -NH-, and -SO_2-;

D is a member selected from the group consisting of:



or A-Y-D is a member selected from the group consisting of:



Wherein R^{1a} is selected from:

hydrogen, Cl, F, Br, Me, OMe, NO_2, CO_2H, CN, $C(=O)NH_2$, and C(=O)OMe;

E is a member selected from the group consisting of:

-N(-H)-C(=O)-and -C(=O)-N(-H)-;

G is $-CR^{7a}R^{8a}-C^{b}R^{8b}$;

wherein R^{7a}, R^{8a}, R^{7b} and R^{8b} are independently a member selected from the group consisting of:

hydrogen, F, Cl, Br, -OH, $-NO_2$, -CN, $-C_{1-4}$alkyl, haloalkyl, $-OR^9$, $-CH_2OR^9$, $-S(=O)_2-R^9$, $-CH_2S(=O)_2-R^9$, $-C(=O)-OR^9$, $-CH_2C(=O)-OR^9$, $-C(=O)-N(R^{9a}, R^{9b})$, $-CH_2C(=O)-N(R^{9a}, R^{9b})$, $-N(R^{9a}, R^{9b})$, $-CH_2N(R^{9a}, R^{9b})$, $-N(R^{9a})-C(=O)-R^{9b}$), phenyl, benzyl, $-C_{0-2}$alkyl-heterocyclic ring system containing from 1-4 heteroatoms selected from the group consisting of O, N and S, wherein the heterocyclic ring system is a 5-6 membered monocyclic ring; wherein the phenyl ring and heterocyclic ring are substituted by a member selected from the group consisting of CH_3, halo, -CN, $-NO_2$, -OMe, $-CO_2H$, $-CO_2Me$;

or R^{7b} and R^{8b} combine to form $CH_2=$, $(CH_3)_2C=$, PhCH=;

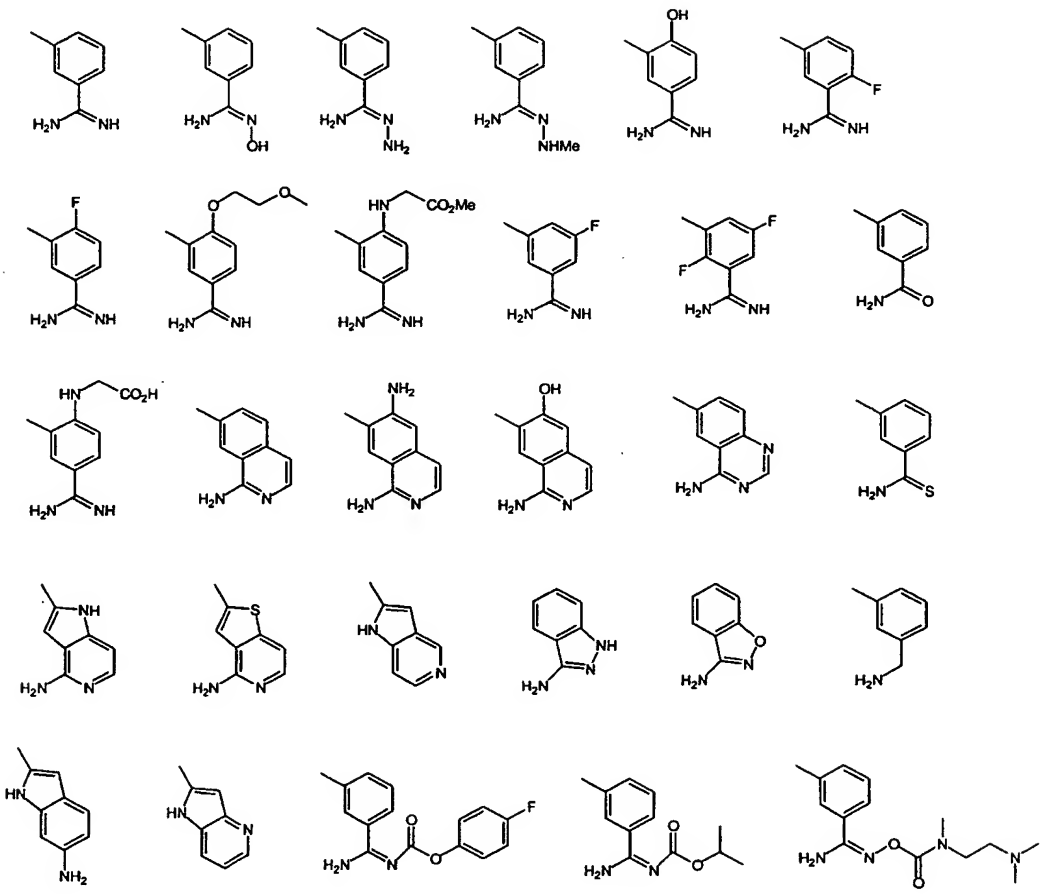
R^9, R^{9a} and R^{9b} are independently selected from:

hydrogen, $-C_{1-4}$alkyl, haloalkyl, phenyl, benzyl; or R^{9a} and R^{9b} may combine with that nitrogen atom to which they are attached to form a 5-6 membered ring which contains from 0-1 additional heteroatoms selected from a group consisting of -N, -O, S;

J is a member selected from the group consisting of:

a direct link, $-CH_2-$;

Z-L is a member selected from the group consisting of:

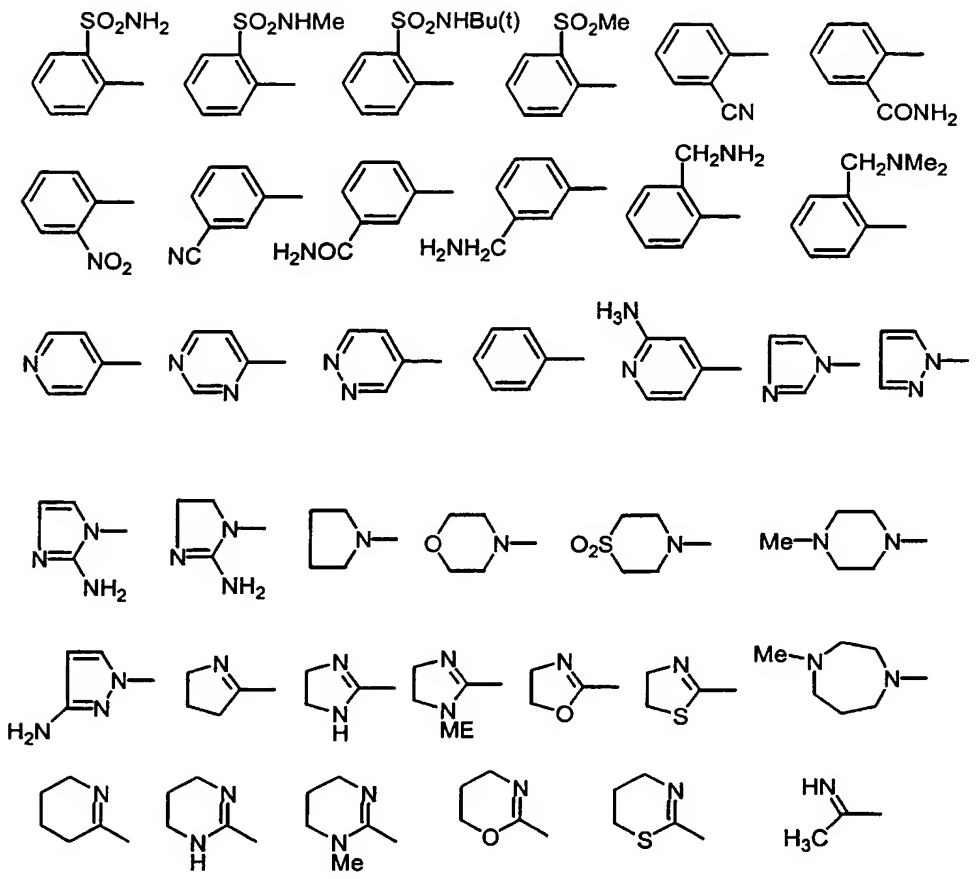


In a further preferred embodiment, the present invention provides a compound according to the formula I:

A-Y-D-E-G-J-Z-L

wherein:

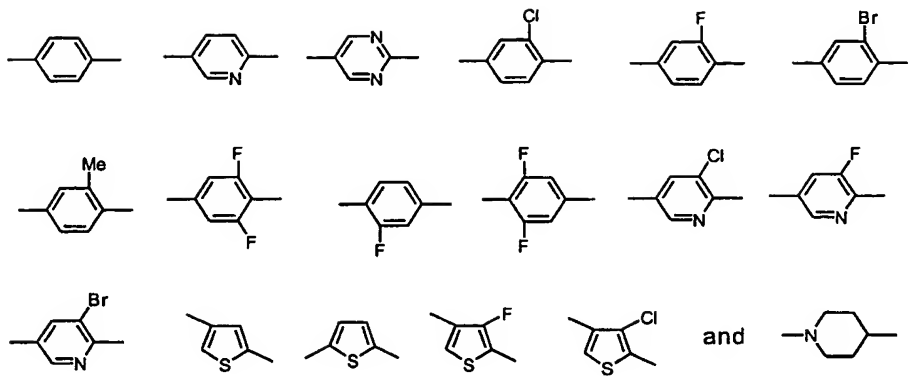
A is a member selected from the group consisting of:



Y is a member selected from the group consisting of:

a direct link, -C(=O)-; -N(-CH_3)-; -N(CH_3)-CH_2-; -C(=NH)-, -CH_2-, –C(=S)-, -NH-, and -SO_2-;

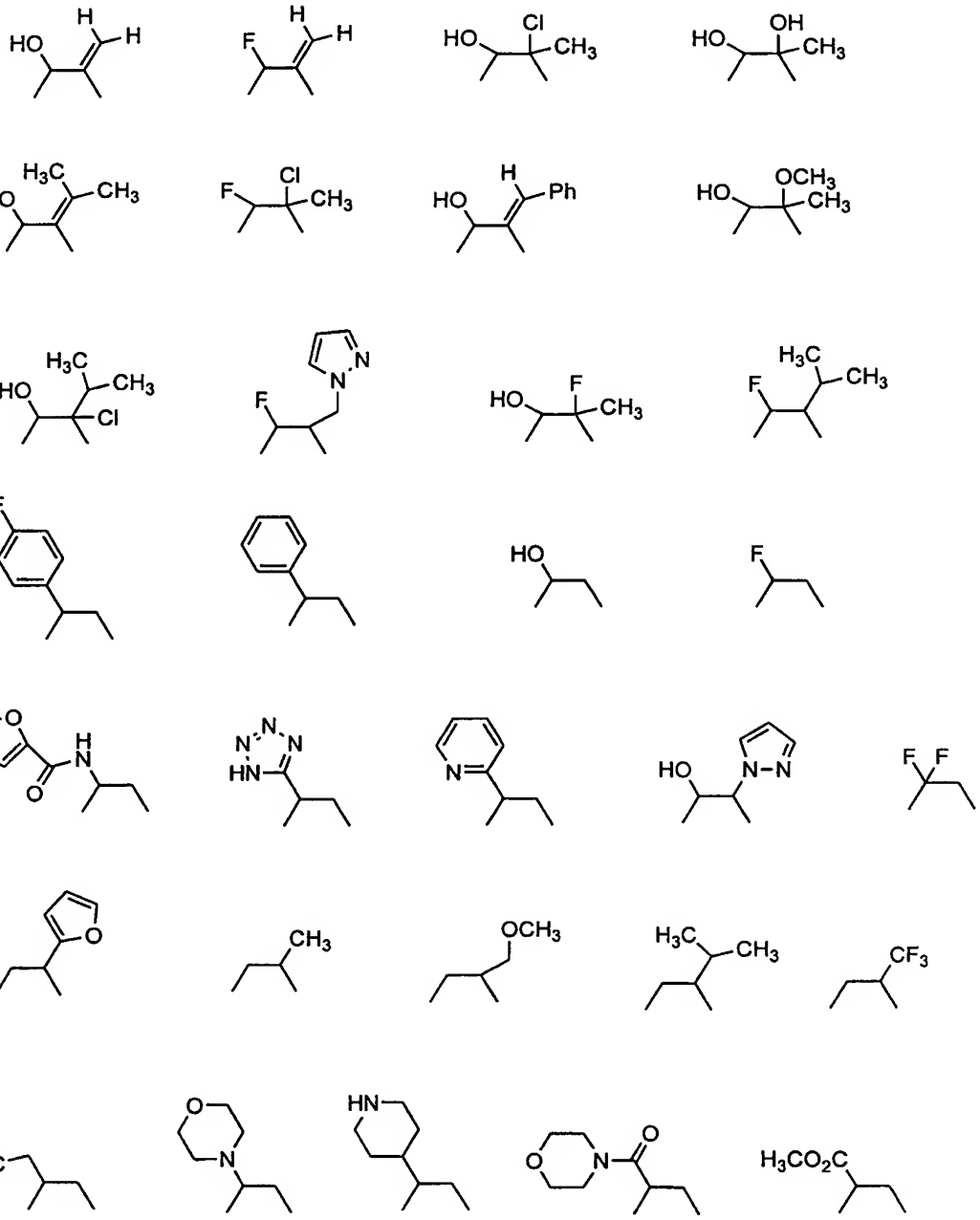
D is a member selected from the group consisting of:



E is a member selected from the group consisting of:

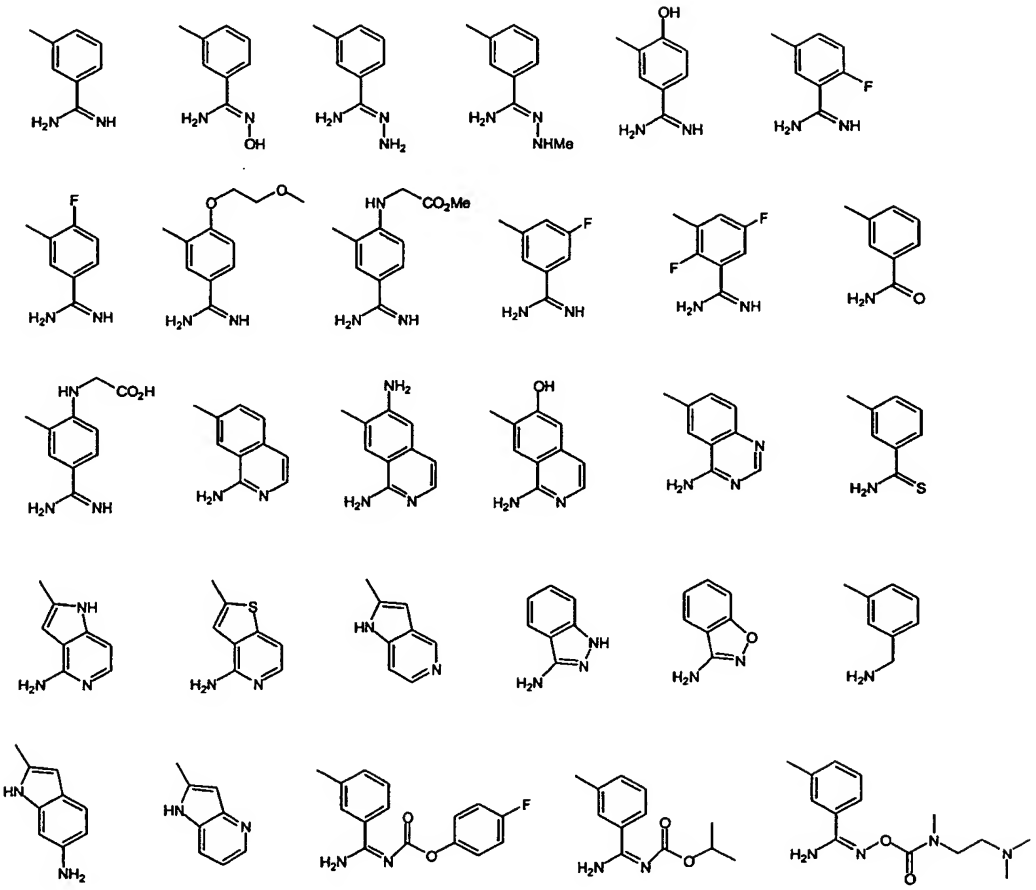
-N(-H)-C(=O)-and -C(=O)-N(-H)-;

G is a member selected from the group consisting of:



J is a direct link;

Z-L is a member selected from the group consisting of:



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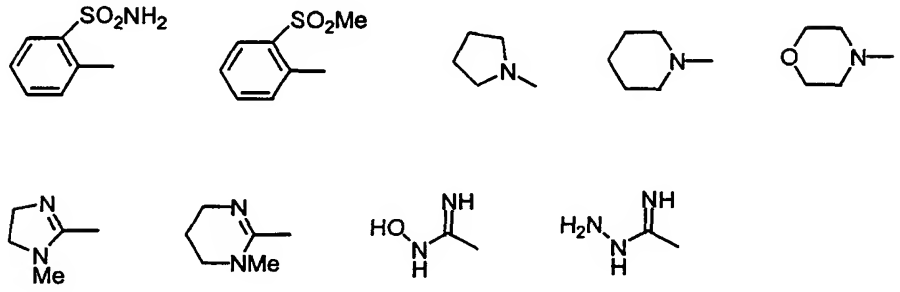
In a further preferred embodiment, the present invention provides a compound according to the formula I:

A-Y-D-E-G-J-Z-L

wherein

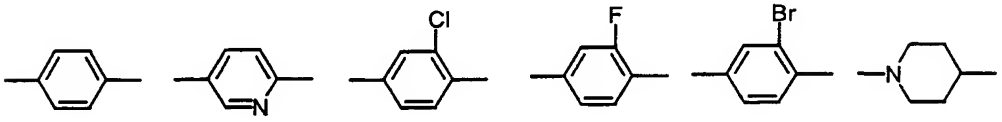
A is a member selected from the group consisting of:



Y is a member selected from the group consisting of:

a direct link, -C(=O)-; -N(-CH_3)-; -N(CH_3)-CH_2-; -C(=NH)-, -CH_2-, –C(=S)-, -NH-, and -SO_2-;

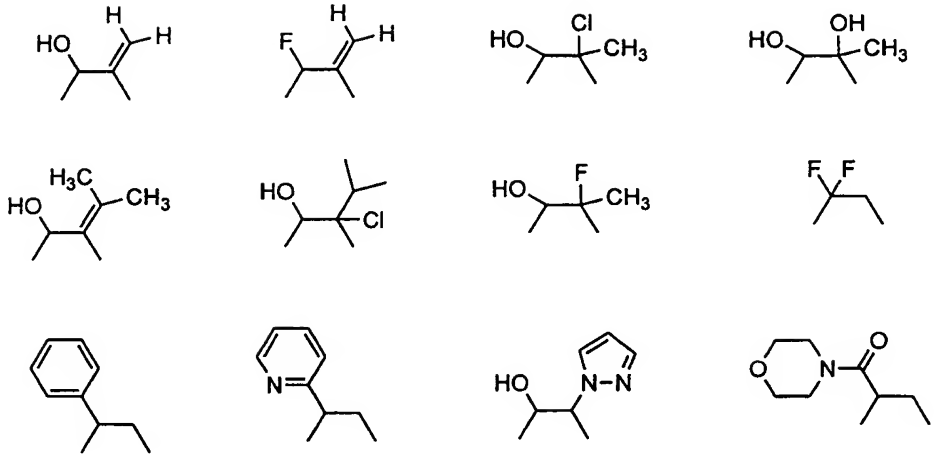
D is a member selected from the group consisting of:



E is a member selected from the group consisting of:

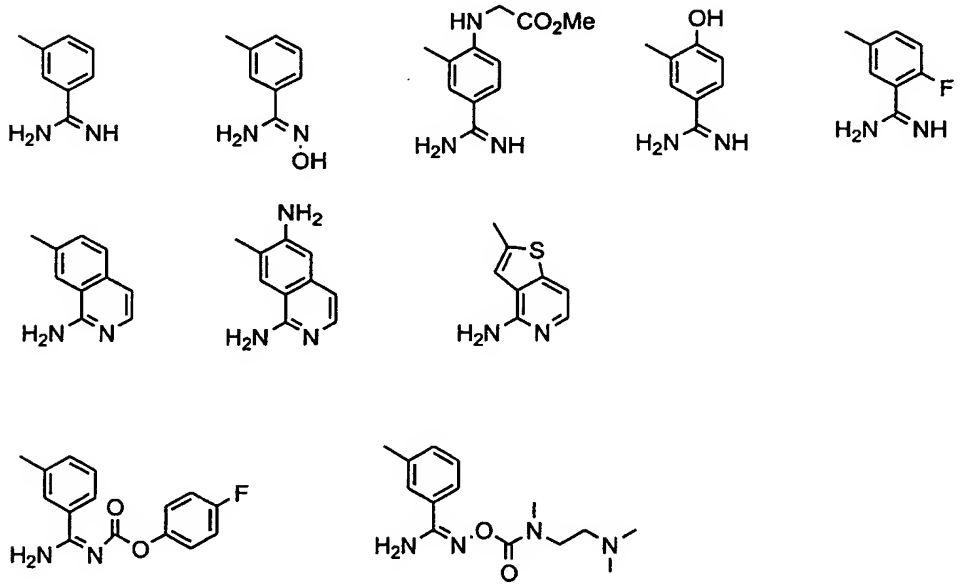
-N(-H)-C(=O)-and -C(=O)-N(-H)-;

G is a member selected from the group consisting of:



J is a direct link;

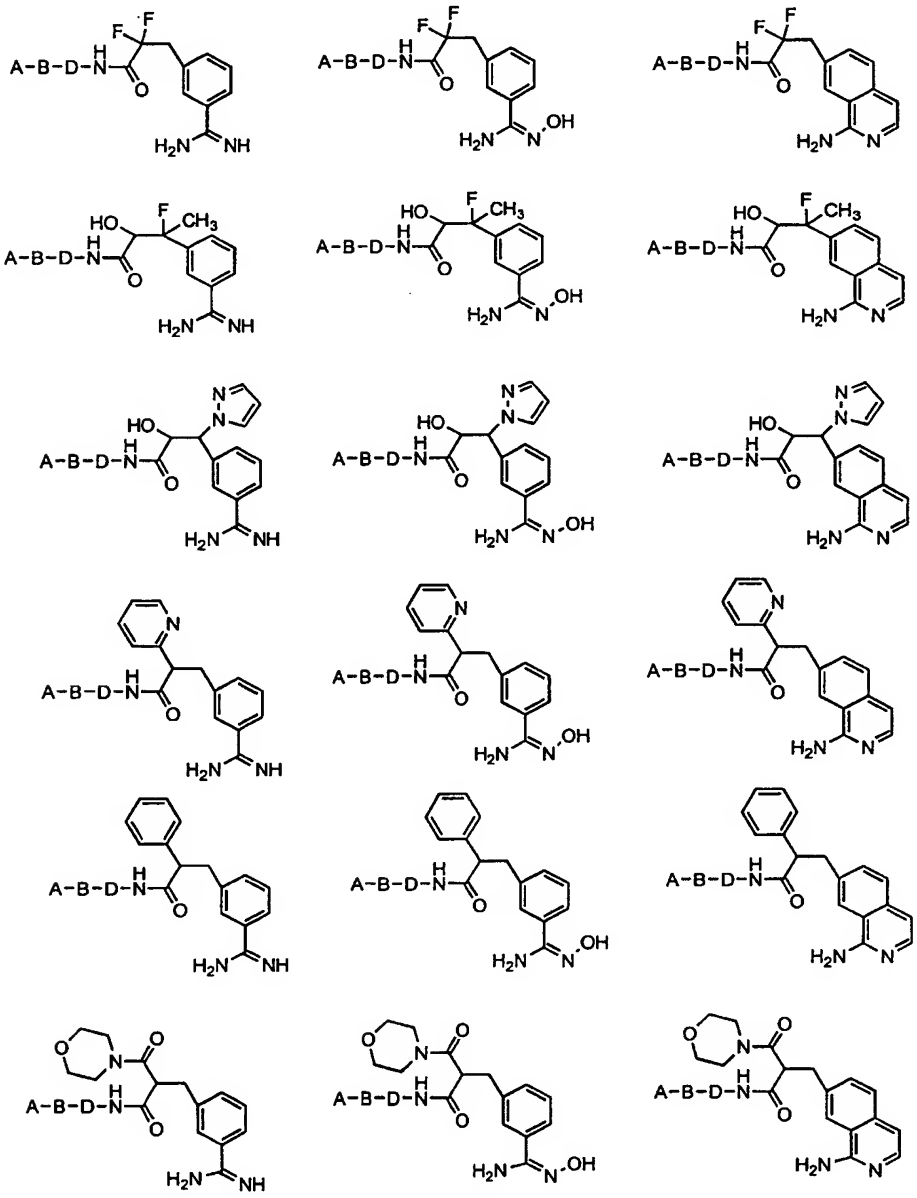
Z-L is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The following non-limiting table illustrates representative compounds of the present invention:

Table of Preferred Compounds



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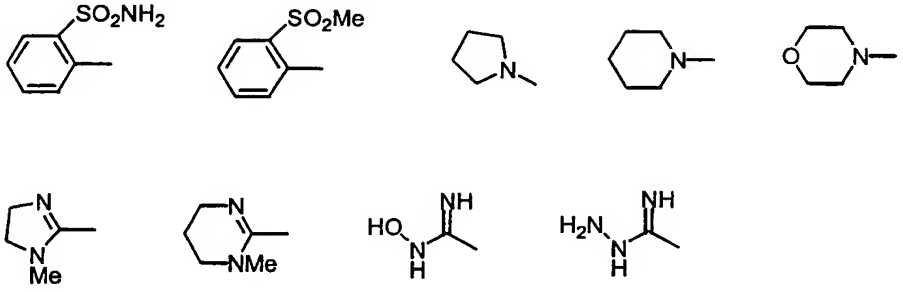
Wherein:

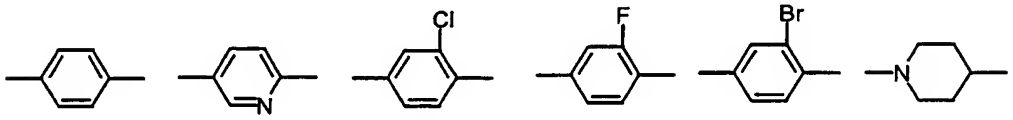
A is a member selected from the group consisting of:



Y is a member selected from the group consisting of:

a direct link, -C(=O)-; -N(-CH_3)-; -N(CH_3)-CH_2-; -C(=NH)-, -CH_2-, –C(=S)-, -NH-, and -SO_2-;

D is a member selected from the group consisting of:



This invention also encompasses all pharmaceutically acceptable isomers, salts, hydrates and solvates of the compounds of the invention. In addition, the compounds can exist in various isomeric and tautomeric forms, and all such forms are meant to be included in the invention, along with pharmaceutically acceptable salts, hydrates and solvates of such isomers and tautomers.

The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, the free acid or free base form of a compound of one of the formulas above can be reacted with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in

which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Prodrug Derivatives of Compounds

This invention also encompasses prodrug derivatives of the compounds contained herein. The term "prodrug" refers to a pharmacologically inactive derivative of a parent drug molecule that requires biotransformation, either spontaneous or enzymatic, within the organism to release the active drug. Prodrugs are variations or derivatives of the compounds of this invention which have groups cleavable under metabolic conditions. Prodrugs become the compounds of the invention which are pharmaceutically active *in vivo*, when they undergo solvolysis under physiological conditions or undergo enzymatic degradation. Prodrug compounds of this invention may be called single, double, triple etc., depending on the number of biotransformation steps required to release the active drug within the organism, and indicating the number of functionalities present in a precursor-type form. Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985 and Silverman, The Organic Chemistry of Drug Design and Drug Action, pp. 352-401, Academic Press, San Diego, CA, 1992). Prodrugs commonly known in the art include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acids with a suitable alcohol, or amides prepared by reaction of the parent acid compound with an amine, or basic groups reacted to form an acylated base derivative. Moreover, the prodrug derivatives of this invention may be combined with other features herein taught to enhance bioavailability.

As mentioned above, the compounds of this invention find utility as therapeutic agents for disease states in mammals which have disorders of coagulation such as in the treatment or prevention of unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, thrombotic stroke, embolic stroke, disseminated intravascular coagulation including the treatment of septic shock, deep venous thrombosis in the prevention of pulmonary embolism or the treatment of reocclusion or restenosis of reperfused coronary arteries. Further, these

compounds are useful for the treatment or prophylaxis of those diseases which involve the production and/or action of factor Xa/prothrombinase complex. This includes a number of thrombotic and prothrombotic states in which the coagulation cascade is activated which include but are not limited to, deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, thromboembolic complications of surgery and peripheral arterial occlusion.

Accordingly, a method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprises administering to the mammal a therapeutically effective amount of a compound of this invention. In addition to the disease states noted above, other diseases treatable or preventable by the administration of compounds of this invention include, without limitation, occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty, thrombus formation in the venous vasculature, disseminated intravascular coagulopathy, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure, hemorrhagic stroke, renal dialysis, blood oxygenation, and cardiac catheterization.

The compounds of the invention also find utility in a method for inhibiting the coagulation biological samples, which comprises the administration of a compound of the invention.

The compounds of the present invention may also be used in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this invention may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of the present invention may act in a synergistic fashion to prevent reocclusion following a successful thrombolytic therapy and/or reduce the time to reperfusion. These compounds may also allow for reduced doses of the thrombolytic agents to be used and therefore minimize potential hemorrhagic side-effects. The compounds of this invention can be utilized *in vivo*, ordinarily in mammals such as primates, (e.g. humans), sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The biological properties of the compounds of the present invention can be readily characterized by methods that are well known in the art, for example by the *in vitro* protease activity assays and *in vivo* studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters, such as are illustrated in the examples.

Diagnostic applications of the compounds of this invention will typically utilize formulations in the form of solutions or suspensions. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrins, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for

therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be 3-11, more preferably 5-9 and most preferably 7-8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as orally, intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally, transdermally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of the invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidinone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, compounds of the invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will be influenced by the route of administration, the therapeutic objectives and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each compound by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be readily determined by one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

The compounds of the invention can be administered orally or parenterally in an effective amount within the dosage range of about 0.1 to 100 mg/kg, preferably about 0.5 to 50 mg/kg and more preferably about 1 to 20 mg/kg on a regimen in a single or 2 to 4 divided daily doses and/or continuous infusion.

Typically, about 5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are binders such as acacia, corn starch or gelatin, and excipients such as microcrystalline cellulose, disintegrating agents like corn starch or alginic acid, lubricants such as magnesium stearate, sweetening agents such as sucrose or lactose, or flavoring agents. When a dosage form is a capsule, in addition to the above

materials it may also contain liquid carriers such as water, saline, or a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

Preparation of Compounds

The compounds of the present invention may be synthesized by either solid or liquid phase methods described and referenced in standard textbooks, or by a combination of both methods. These methods are well known in the art. See, Bodanszky, "The Principles of Peptide Synthesis", Hafner, *et al.*, Eds., Springer-Verlag, Berlin, 1984.

Starting materials used in any of these methods are commercially available from chemical vendors such as Aldrich, Sigma, Nova Biochemicals, Bachem Biosciences, and the like, or may be readily synthesized by known procedures.

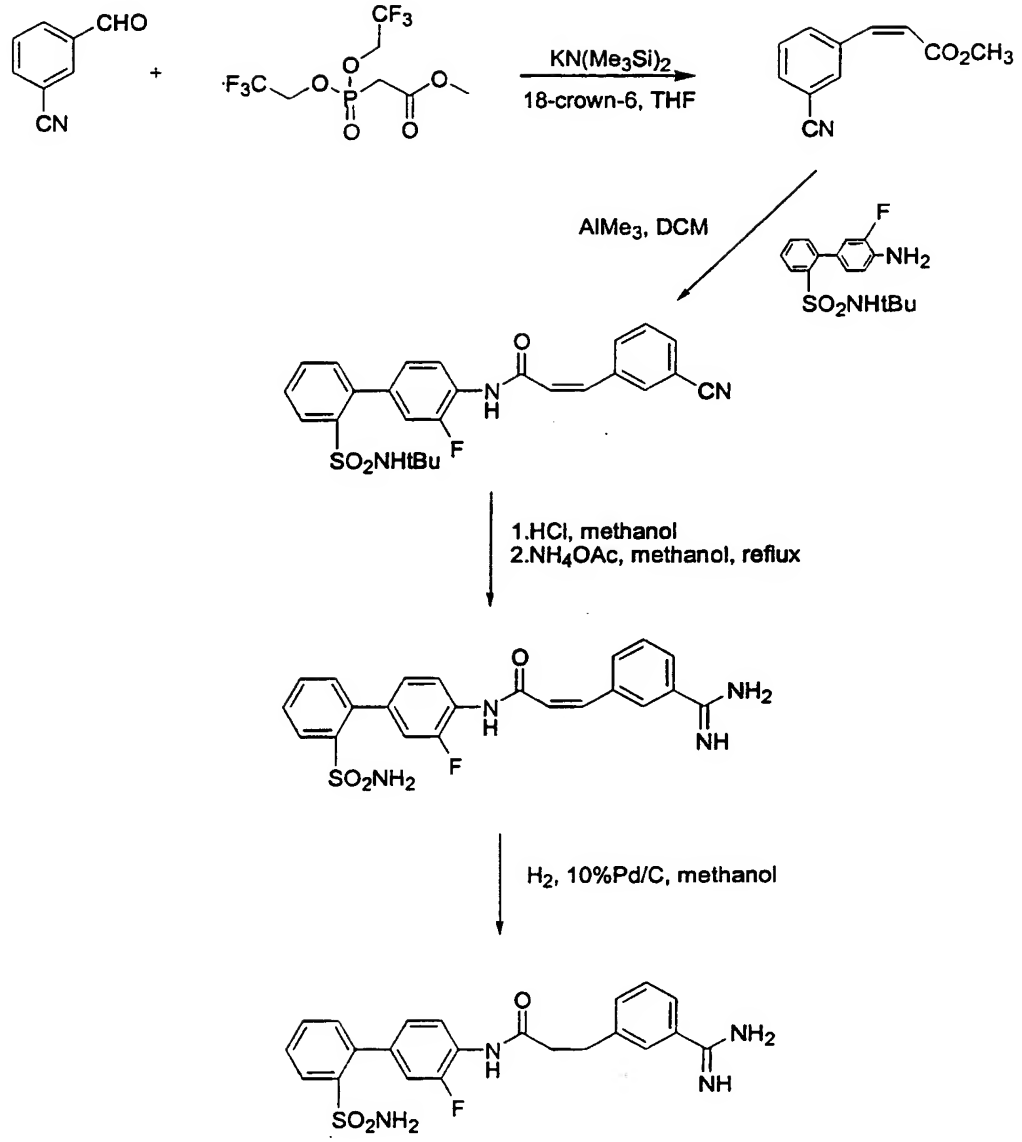
Reactions are carried out in standard laboratory glassware and reaction vessels under reaction conditions of standard temperature and pressure, except where otherwise indicated.

During the synthesis of these compounds, the functional groups of the amino acid derivatives used in these methods are protected by blocking groups to prevent cross reaction during the coupling procedure. Examples of suitable blocking groups and their use are described in "The Peptides: Analysis, Synthesis, Biology", Academic Press, Vol. 3 (Gross, *et al.*, Eds., 1981) and Vol. 9 (1987), the disclosures of which are incorporated herein by reference.

Non-limiting exemplary synthesis schemes are outlined directly below, and specific steps are described in the Examples. The reaction products are isolated and purified by conventional methods, typically by solvent extraction into a compatible solvent. The products may be further purified by column chromatography or other

appropriate methods.

Scheme 1



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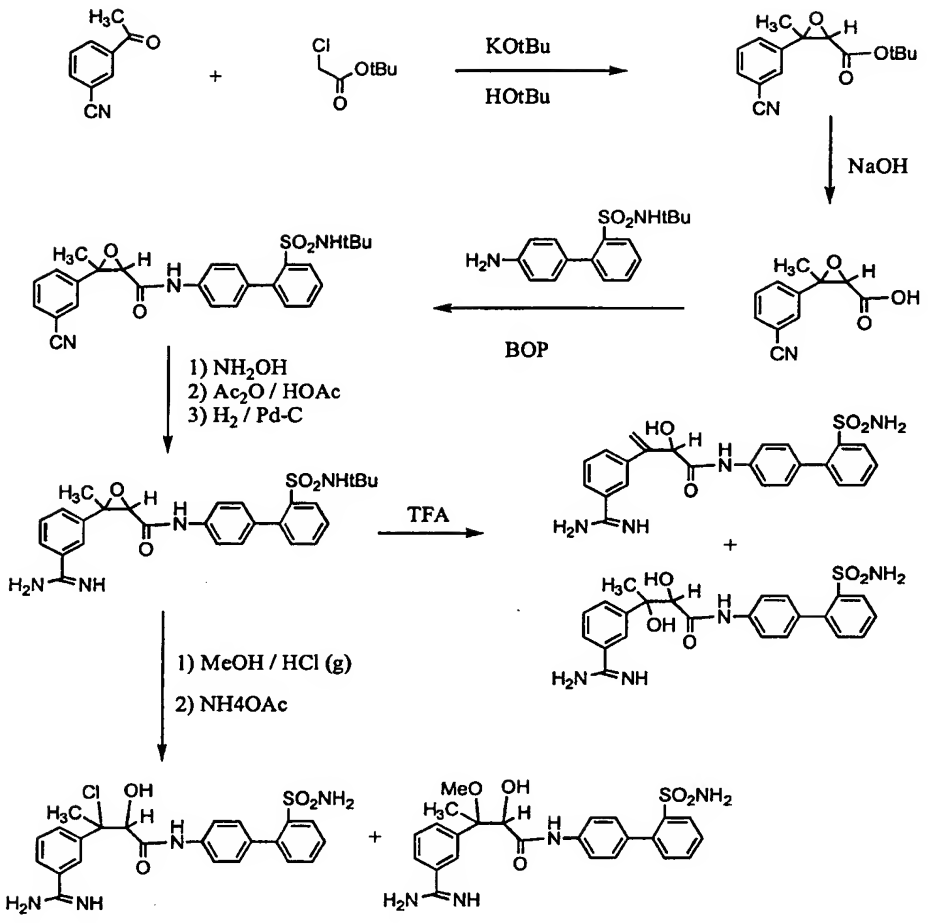
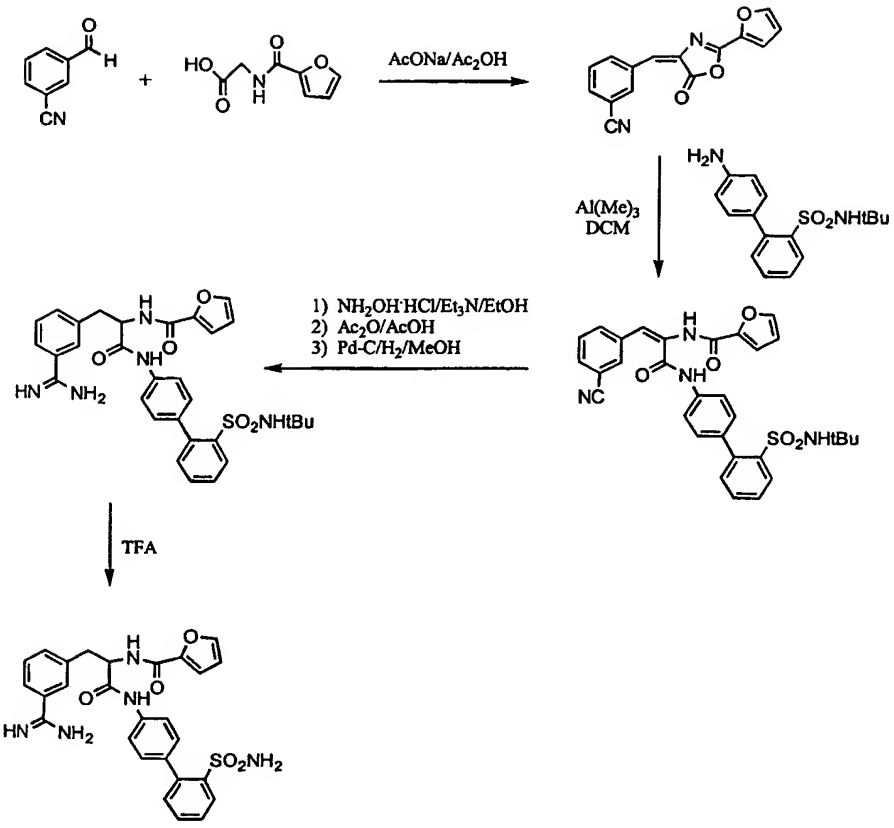
Scheme 2


KOtBu
HOtBu
NaOH
BOP
1) NH2OH
2) Ac2O / HOAc
3) H2 / Pd-C
TFA
1) MeOH / HCl (g)
2) NH4OAc

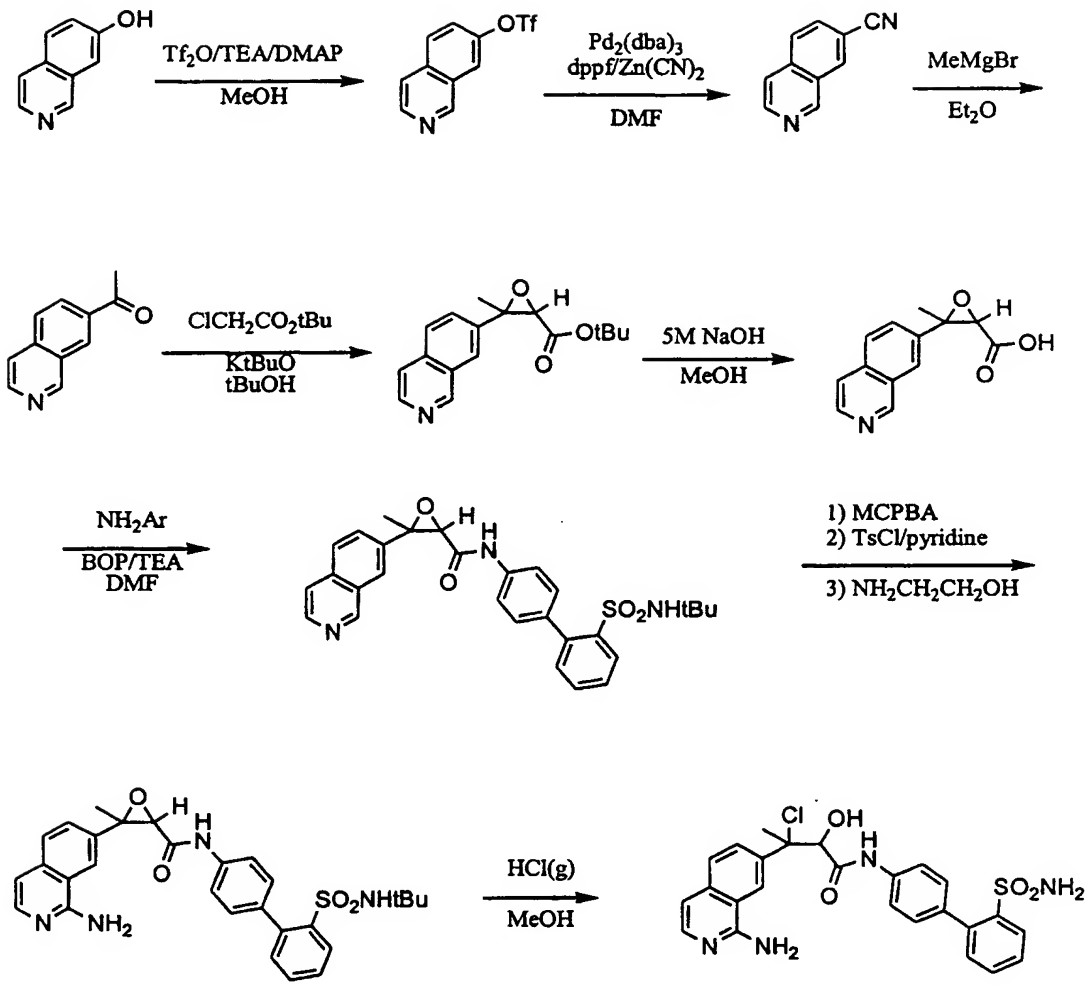
Scheme3


AcONa/Ac2OH
Al(Me)3
DCM
1) NH2OH·HCl/Et3N/EtOH
2) Ac2O/AcOH
3) Pd-C/H2/MeOH
TFA
CN
NC
SO2NHtBu
SO2NH2

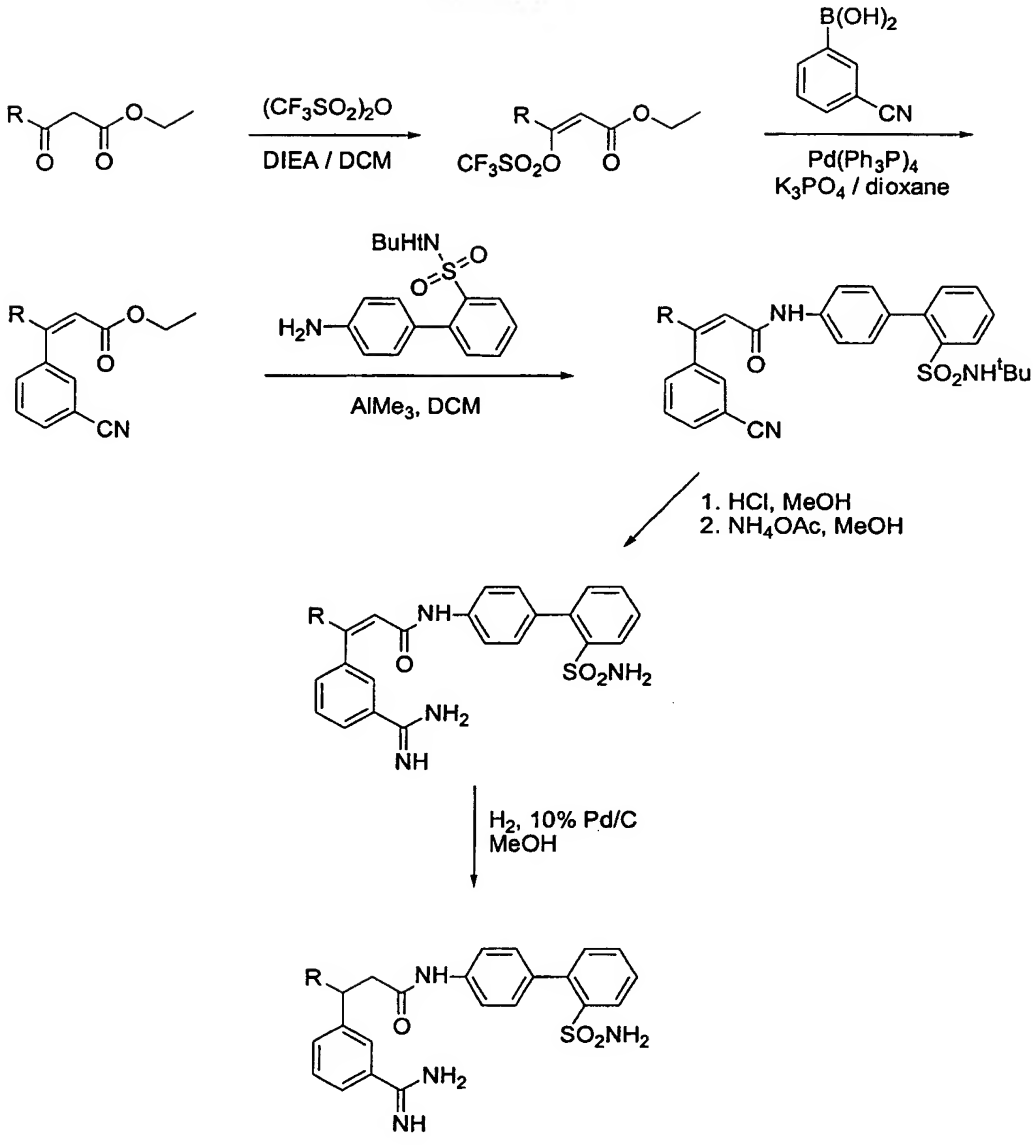
5

Scheme 4

5


OH
Tf2O/TEA/DMAP
MeOH
OTf
Pd2(dba)3
dppf/Zn(CN)2
DMF
CN
MeMgBr
Et2O
ClCH2CO2tBu
KtBuO
tBuOH
OtBu
5M NaOH
MeOH
OH
NH2Ar
BOP/TEA
DMF
SO2NHtBu
1) MCPBA
2) TsCl/pyridine
3) NH2CH2CH2OH
NH2
HCl(g)
MeOH
Cl
SO2NH2

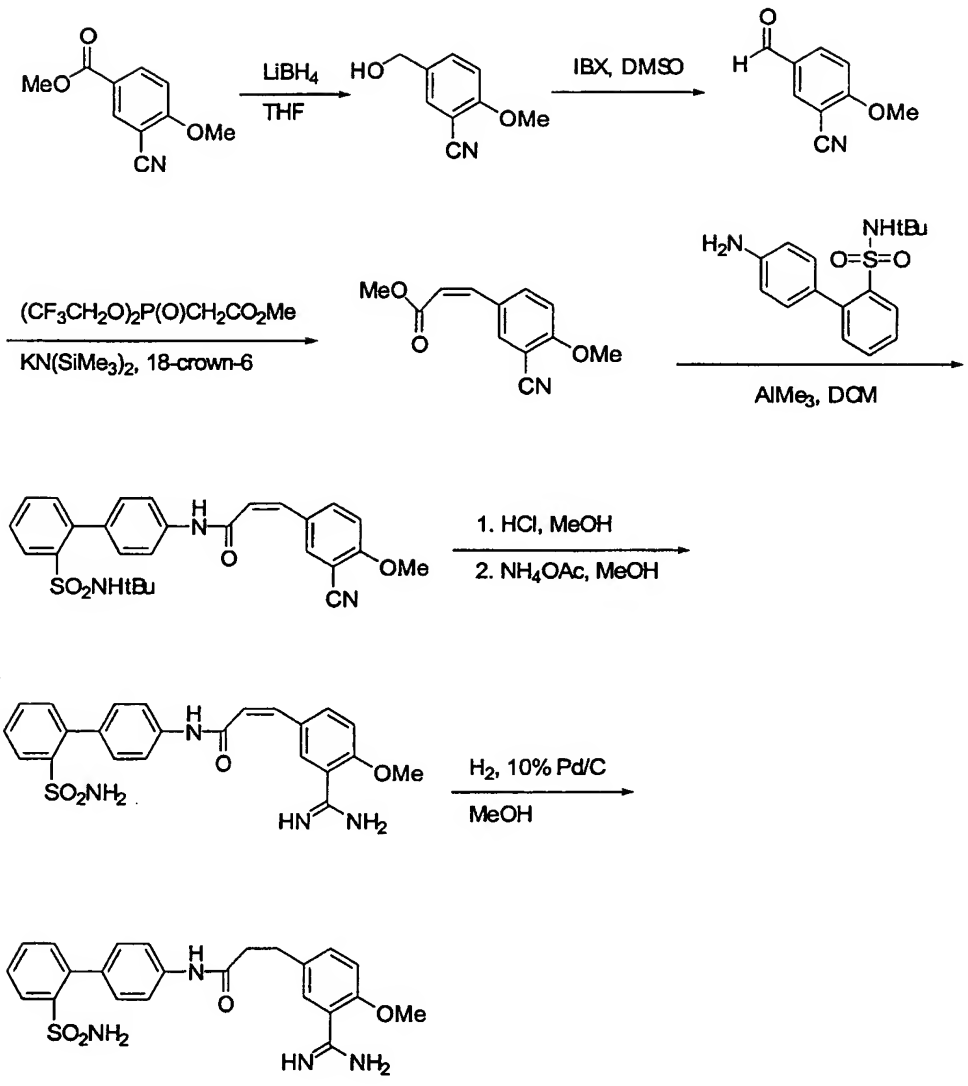
Scheme 5


R
O
O
$(CF_3SO_2)_2O$
DIEA / DCM
CF_3SO_2O
$B(OH)_2$
CN
$Pd(Ph_3P)_4$
K_3PO_4 / dioxane
BuHtN
H_2N
$AlMe_3$, DCM
NH
SO_2NH^tBu
1. HCl, MeOH
2. NH_4OAc, MeOH
SO_2NH_2
NH_2
H_2, 10% Pd/C
MeOH

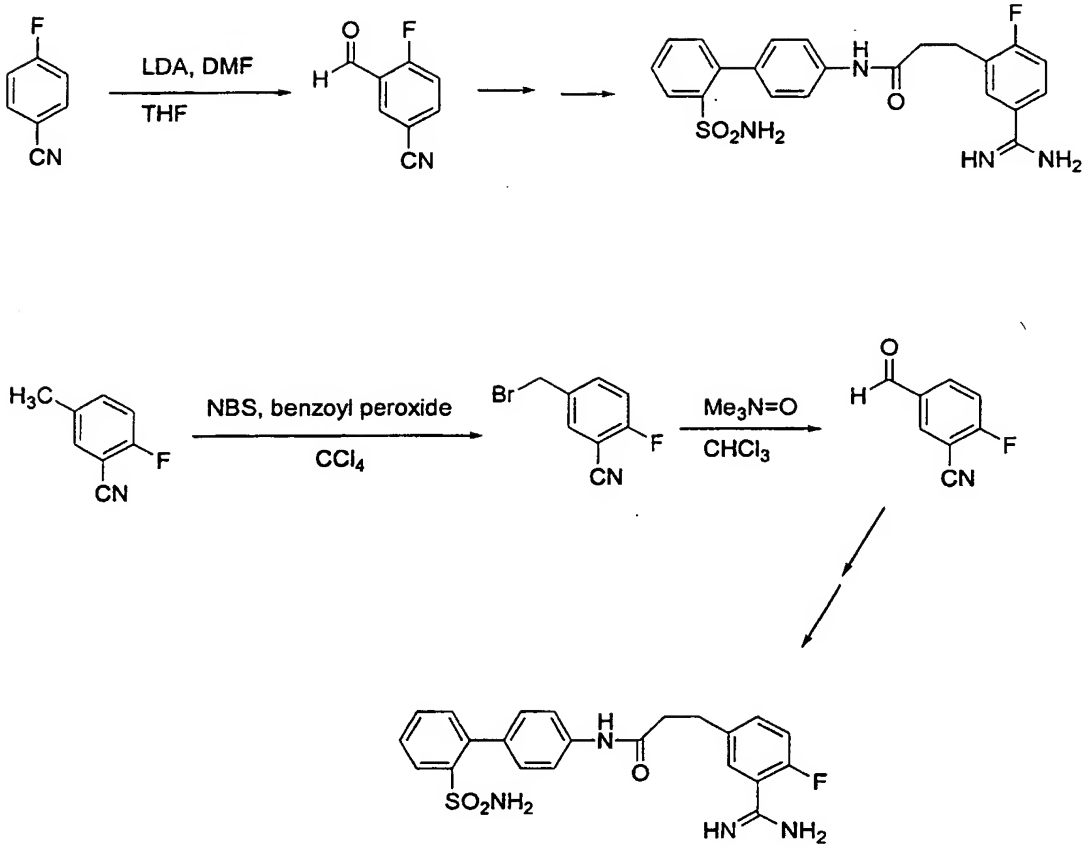
5

Scheme 6

5

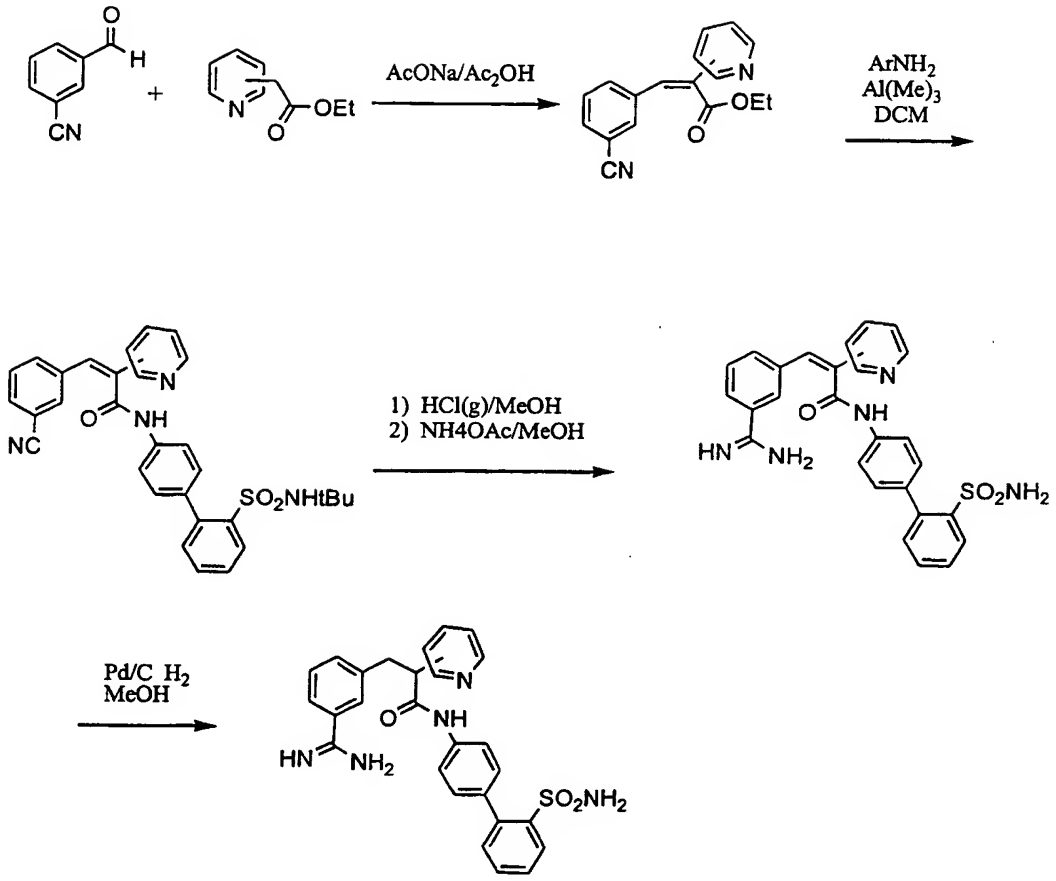

MeO
O
OMe
CN
LiBH4
THF
HO
IBX, DMSO
H
(CF3CH2O)2P(O)CH2CO2Me
KN(SiMe3)2, 18-crown-6
H2N
NHtBu
O=S=O
AlMe3, DCM
SO2NHtBu
1. HCl, MeOH
2. NH4OAc, MeOH
SO2NH2
HN
NH2
H2, 10% Pd/C
MeOH

Scheme 7

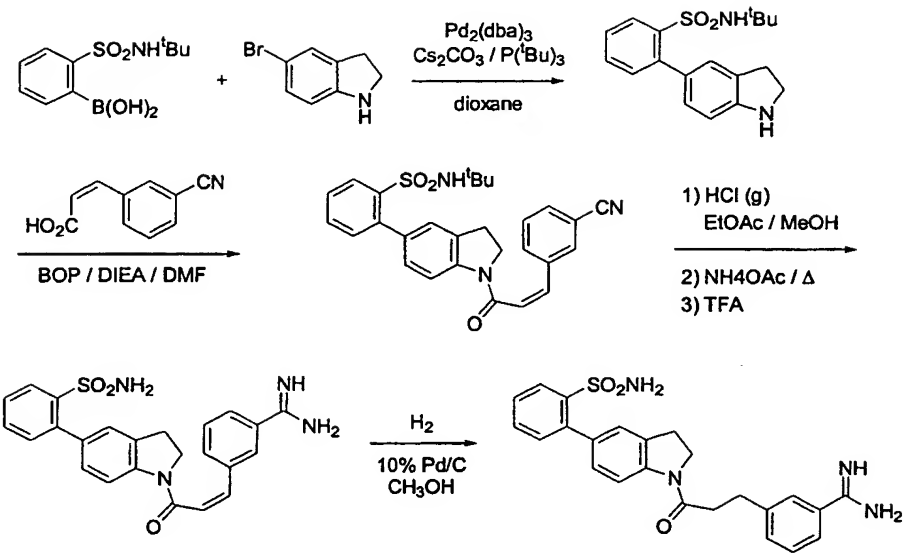

F
CN
LDA, DMF
THF
O
H
F
CN
F
H
N
O
SO2NH2
HN
NH2
H3C
F
CN
NBS, benzoyl peroxide
CCl4
Br
F
CN
Me3N=O
CHCl3
O
H
F
CN
H
N
O
F
SO2NH2
HN
NH2

5

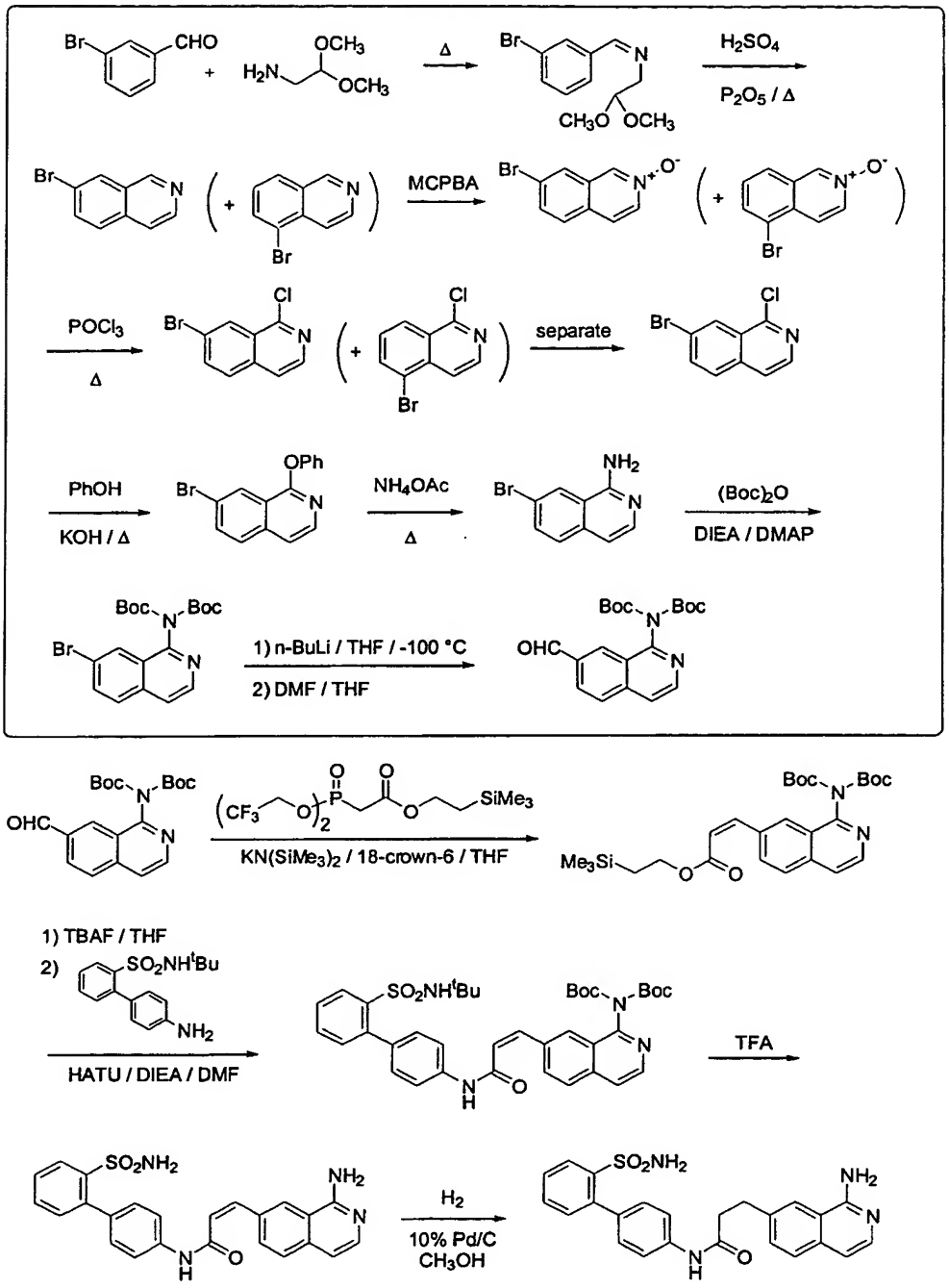
Scheme 8


AcONa/Ac2OH
ArNH2
Al(Me)3
DCM
1) HCl(g)/MeOH
2) NH4OAc/MeOH
Pd/C H2
MeOH

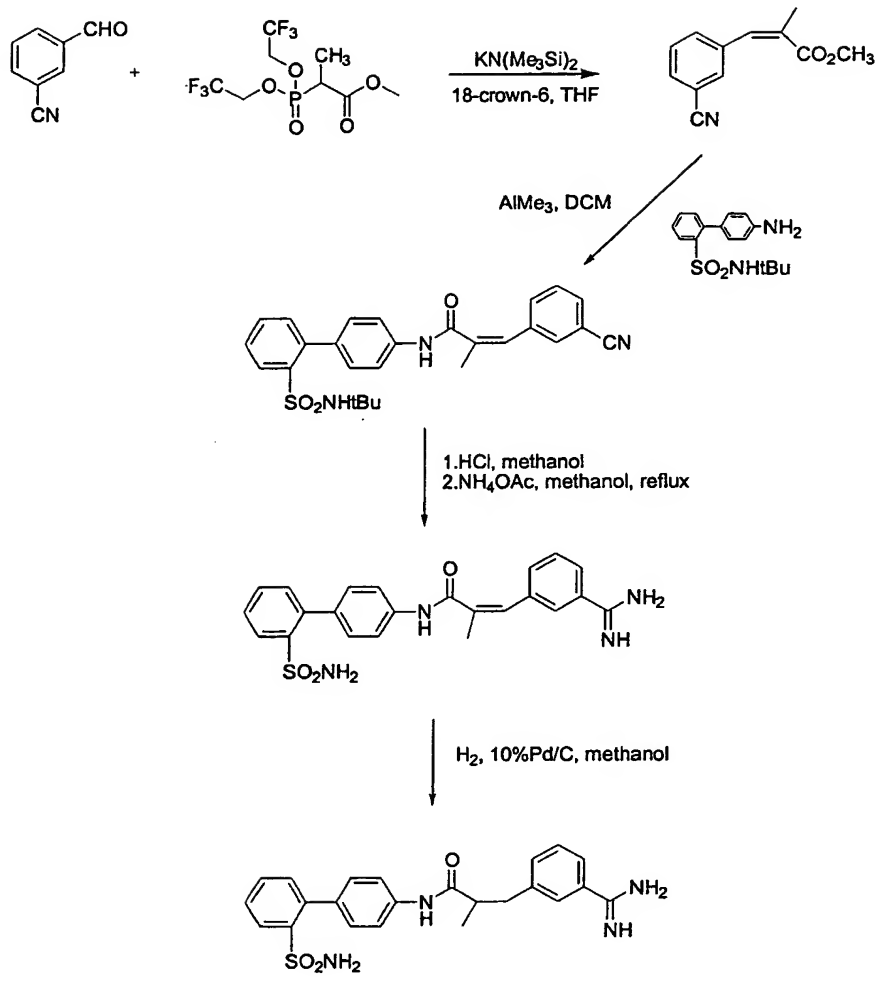
Scheme 9


SO2NHtBu
B(OH)2
Br
N
H
Pd2(dba)3
Cs2CO3 / P(tBu)3
dioxane
SO2NHtBu
N
H
CN
HO2C
BOP / DIEA / DMF
SO2NHtBu
CN
N
O
1) HCl (g)
EtOAc / MeOH
2) NH4OAc / Δ
3) TFA
SO2NH2
NH
NH2
N
O
H2
10% Pd/C
CH3OH
SO2NH2
N
O
NH
NH2

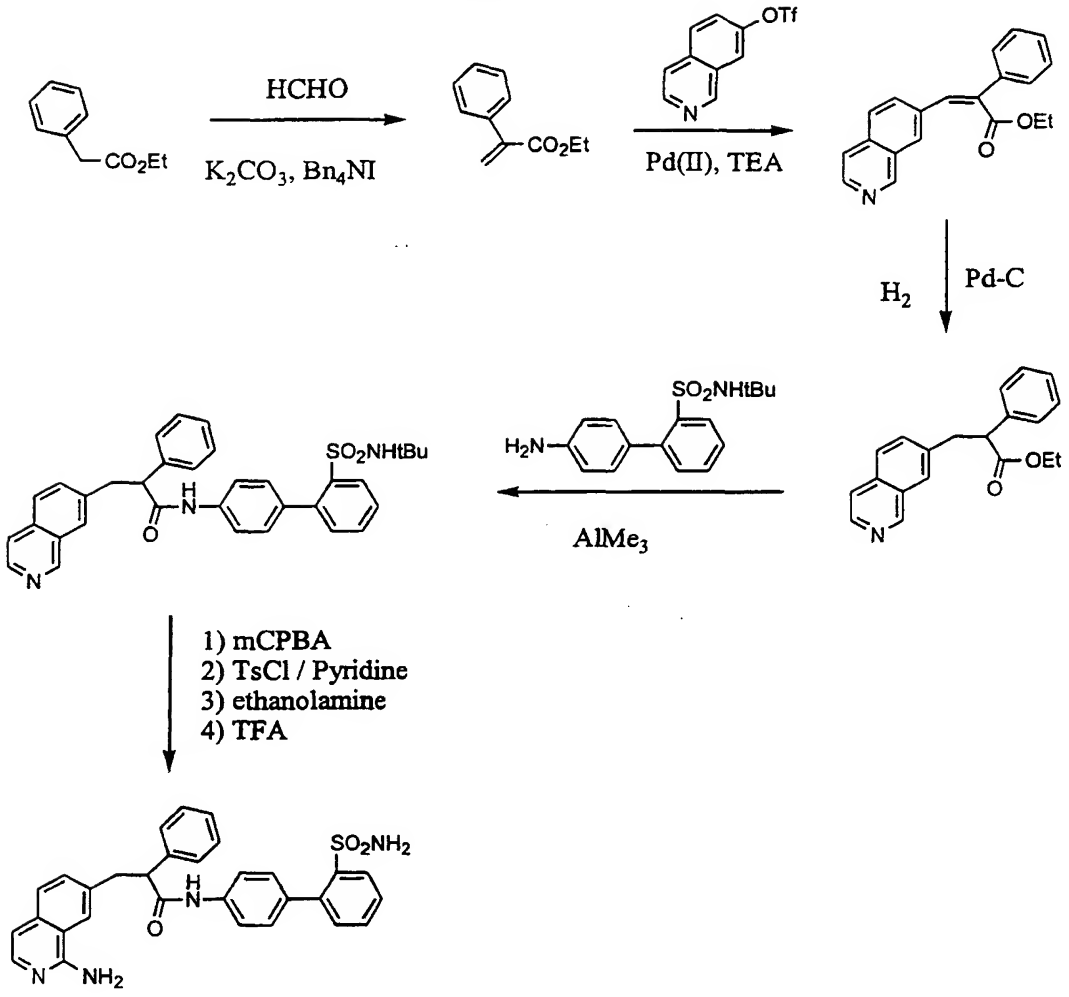
Scheme 10


Br
CHO
+
H2N
OCH3
OCH3
Δ
N
CH3O
OCH3
H2SO4
P2O5 / Δ
MCPBA
N+
O-
POCl3
Cl
separate
PhOH
KOH / Δ
OPh
NH4OAc
NH2
(Boc)2O
DIEA / DMAP
Boc
1) n-BuLi / THF / -100 °C
2) DMF / THF
OHC
CF3
SiMe3
KN(SiMe3)2 / 18-crown-6 / THF
Me3Si
1) TBAF / THF
2)
SO2NHtBu
HATU / DIEA / DMF
TFA
SO2NH2
H2
10% Pd/C
CH3OH

Scheme 11


CHO
CN
CF3
CH3
F3C
O
P
O
O
O
KN(Me3Si)2
18-crown-6, THF
CO2CH3
CN
AlMe3, DCM
NH2
SO2NHtBu
O
N
H
CN
SO2NHtBu
1.HCl, methanol
2.NH4OAc, methanol, reflux
NH2
NH
SO2NH2
H2, 10%Pd/C, methanol
NH2
NH
SO2NH2

Scheme 12



Compositions and Formulations

The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts

are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, reaction of the free acid or free base form of a compound of the structures recited above with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Diagnostic applications of the compounds of this invention will typically utilize formulations such as solution or suspension. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with

physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinalpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrins, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders,

aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of this invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the factor Xa inhibitors of this invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will naturally be influenced by the route of administration, the therapeutic objectives, and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each inhibitor by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be within the ambit of one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

A typical dosage might range from about 0.001 mg/kg to about 1000 mg/kg, preferably from about 0.01 mg/kg to about 100 mg/kg, and more preferably from about 0.10 mg/kg to about 20 mg/kg. Advantageously, the compounds of this invention may be administered several times daily, and other dosage regimens may also be useful.

Typically, about 0.5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder,

preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are a binder such as acacia, corn starch or gelatin, and excipient such as microcrystalline cellulose, a disintegrating agent like corn starch or alginic acid, a lubricant such as magnesium stearate, a sweetening agent such as sucrose or lactose, or a flavoring agent. When a dosage form is a capsule, in addition to the above materials it may also contain a liquid carrier such as water, saline, a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

In practicing the methods of this invention, the compounds of this invention may be used alone or in combination, or in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this inventions may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice, such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of this invention can be utilized in vivo, ordinarily in mammals such as primates, such as humans, sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The preferred compounds of the present invention are characterized by their ability to inhibit thrombus formation with acceptable effects on classical measures of coagulation parameters, platelets and platelet function, and acceptable levels of bleeding complications associated with their use. Conditions characterized by undesired thrombosis would include those involving the arterial and venous vasculature.

With respect to the coronary arterial vasculature, abnormal thrombus formation characterizes the rupture of an established atherosclerotic plaque which is the major cause of acute myocardial infarction and unstable angina, as well as also characterizing the occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA).

With respect to the venous vasculature, abnormal thrombus formation characterizes the condition observed in patients undergoing major surgery in the lower extremities or the abdominal area who often suffer from thrombus formation in the venous vasculature resulting in reduced blood flow to the affected extremity and a predisposition to pulmonary embolism. Abnormal thrombus formation further characterizes disseminated intravascular coagulopathy commonly occurs within both vascular systems during septic shock, certain viral infections and cancer, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure.

The compounds of this present invention, selected and used as disclosed herein, are believed to be useful for preventing or treating a condition characterized by undesired thrombosis, such as (a) the treatment or prevention of any thrombotically mediated acute coronary syndrome including myocardial infarction,

unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, (b) the treatment or prevention of any thrombotically mediated cerebrovascular syndrome including embolic stroke, thrombotic stroke or transient ischemic attacks, (c) the treatment or prevention of any thrombotic syndrome occurring in the venous system including deep venous thrombosis or pulmonary embolus occurring either spontaneously or in the setting of malignancy, surgery or trauma, (d) the treatment or prevention of any coagulopathy including disseminated intravascular coagulation (including the setting of septic shock or other infection, surgery, pregnancy, trauma or malignancy and whether associated with multi-organ failure or not), thrombotic thrombocytopenic purpura, thromboangiitis obliterans, or thrombotic disease associated with heparin induced thrombocytopenia, (e) the treatment or prevention of thrombotic complications associated with extracorporeal circulation (e.g. renal dialysis, cardiopulmonary bypass or other oxygenation procedure, plasmapheresis), (f) the treatment or prevention of thrombotic complications associated with instrumentation (e.g. cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve), and (g) those involved with the fitting of prosthetic devices.

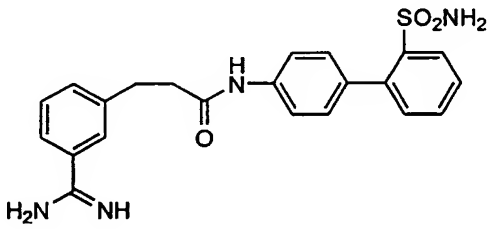
Anticoagulant therapy is also useful to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus the compounds of this invention can be added to or contacted with any medium containing or suspected to contain factor Xa and in which it is desired that blood coagulation be inhibited, e.g., when contacting the mammal's blood with material such as vascular grafts, stents, orthopedic prostheses, cardiac stents, valves and prostheses, extra corporeal circulation systems and the like.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make

and utilize the compounds of the present invention and practice the claimed methods. The following working examples therefore, specifically point out preferred embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

EXAMPLES

Example 1. Preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-(3-amidinophenyl)-propionamide.



A. Preparation of N-tert-butyl benzenesulfonamide

To a solution of tert-butylamine (5.73g, 78.4mmol) and triethylamine (16.6ml, 119mmol) in dichloromethane (200ml) in an ice bath was added benzenesulfonyl chloride (13.85g, 78.4mmol) dropwise. The mixture was stirred at room temperature overnight. It was washed with saturated sodium carbonate (60ml) and brine (60ml). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2x50ml). The combined organic extracts were dried over magnesium sulfate. The solvent was evaporated *in vacuo* to give the title compound as a light yellowish solid (15.92g, 95%). ES-MS (M+H)+ = 214.

B. Preparation of 2-(tert-butylaminosulfonyl)-benzeneboronic acid.

To a solution of N-tert-butyl benzenesulfonamide (15.92g, 74.7mmol) in tetrahydrofuran (200ml) in an ice bath was added 1.6M n-butyllithium in hexane (100ml, 164mmol) dropwise over 30 minutes. The mixture remained a clear solution. In an ice bath it was added triisopropylborate (24.1ml, 104mmol) dropwise. The mixture was stirred at room temperature for 3.5hrs, solution

becoming cloudy. After it was cooled in an ice bath, 1N hydrochloride (200ml) was added. The mixture was stirred at room temperature overnight. It was extracted with ether (2x50ml). The organic extract was washed with 1N sodium hydroxide (2x60ml). The aqueous solution was acidified to pH=1 with 6N hydrochloride, and then extracted with ether (2x100ml). The ether extract was dried over magnesium sulfate, and concentrated *in vacuo* to give the title compound as a while solid (11.5g, 60%). ES-MS (M+H)+ = 258.

C. Preparation of 4-[(2-tert-butylaminosulfonyl)phenyl]-aniline

To a solution of 2-(tert-butylaminosulfonyl)-benzeneboronic acid (6.00g, 23.35mmol) in 120ml toluene was added water (16ml), isopropanol (60ml), and NaOH (40ml, 5M aqueous solution). To this were added 4-bromoaniline and Pd(Ph3P)4. This heterogeneous mixture is then refluxed for 6hr, then stirred at room temperature over night before refluxing for another 1.5hr. The reaction mixture is then partitioned between water and ethyl acetate. The aqueous layer is extracted twice with ethyl acetate. The organic layers are then dried over MgSO4, filtered and concentrated in vacuo. The crude residue is purified by silica gel flash chromatography. The desired product can be eluded with 30% ethyl acetate in hexanes and concentrated to give an orange solid (5.06g, 16.65, 71%). ES-MS(M+H)+=305.

D. Preparation of (Z) methyl 3-cyanocinnamate

To a solution of bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl) phosphonate (1.00 g, 3.14 mmol) and 18-crown-6 (4.14 g, 15.7 mmol) in THF (50 mL) at -78 C, potassium bis(trimethylsilyl)amide (6.3 mL, 0.5 M in toluene, 3.15 mmol) was added dropwise. After the addition was completed, 3-cyanobenzaldehyde (0.412 g, 3.14 mmol) in THF (8 mL) was added. The mixture was stirred at – 78 C for 30 min before it was quenched with aq. NH4Cl. Water and ether were added. Aqueous phase was separated, extracted with ether once more. The combined organic solutions were dried over Na2SO4, concentrated in vacuo to give a solid, which was purified by a silica gel column, first eluted with EtOAc/hexane (5/95), then with EtOAc/hexane (10/90) to give the titled compound (0.40 g) (yield: 68%). MS 188 (M + H).

E. Preparation of (2Z)-N-[4-(2-[(tert-butylamino)sulfonyl]phenyl)phenyl]-3-(3-cyanophenyl)-acrylamide.

To a solution of 4-(2'-tert-butylaminosulfonylphenyl)aniline (80 mg, 0.263 mmol) in CH2Cl2 (4 mL) at room temperature, trimethylaluminum (0.39 mL, 2.0 M in hexane, 0.78 mmol) was added dropwise. After the solution was stirred for 30 min at room temperature, compound (Z) methyl 3-cyanocinnamate (50 mg, 0.267 mmol) was added. The mixture was stirred at room temperature for 2 days. The solution was neutralized with 1N HCl (10 mL) to pH = 1-2. Water and CH2Cl2 were added, and organic phase was separated, dried over Na2SO4, concentrated in vacuo to give a yellowish soild (120 mg) (yield: 98%), which was sufficiently pure to be used in the following reaction. MS 482 (M + Na)

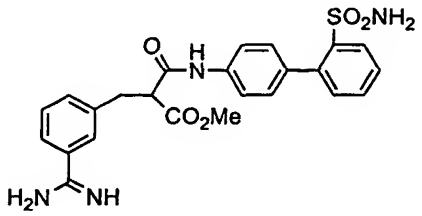
F. Preparation of (2Z)-N-{4-[(2-aminosulfonyl)phenyl]phenyl}-3-(3-amidinophenyl)-acrylamide.

To a solution of compound (2Z)-N-[4-(2-[(tert-butylamino)sulfonyl]phenyl)phenyl]-3-(3-cyanophenyl)-acrylamide (120 mg, 0.261 mmol) in anhydrous MeOH cooled in ice bath, hydrogen chloride gas was bubbled to saturation. The solution was then stirred at room temperature overnight. It was concentrated in vacuo, the residue was dissolved in anhydrous MeOH (4 mL). To the solution, NH4OAc (120 mg, 1.56 mmol) was added. The mixture was heated to reflux for 0.5 h. It was concentrated in vacuo. The residue was purified by HPLC using a gradient of 5% CH3CN in H2O (containing 0.1% TFA) to 80% CH3CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (50 mg) (yield: 46%). MS 421 (M + H)

G. Preparation of N-{4-[(2-aminosulfonyl)phenyl]phenyl}-3-(3-amidinophenyl)-propionamide.

A solution of compound (2Z)-N-[4-(2-[(tert-butylamino)sulfonyl]phenyl)phenyl]-3-(3-cyanophenyl)-acrylamide (12 mg, 22 μmol) and Pd-C (5%, 6 mg) in MeOH (2 mL) was hydrogenated in a Parr Shaker under 50 psi overnight. The solution was then filtered through a plug of celite. The filtrate was concentrated in vacuo to give the titled compound (12 mg) (yield: 99%). MS 423 (M + H)

Example 2. Preparation of N-{4-[(2-aminosulfonyl)phenyl]phenyl}-2-methoxycarbonyl-3-(3-amidinophenyl)-propionamide.



A. Preparation of (2E) and (2Z) tert-butyl 2-methoxycarbonyl-3-(3-cyanophenyl)-acrylate.

To a solution of 3-cyanobenzaldehyde (0.700 g, 5.34 mmol) and t-butyl methyl malonate (0.845 mL, 5.00 mmol) in toluene (40 mL), piperidine (0.500 mL, 5.06 mmol) was added. The mixture was heated to reflux overnight. Dean-Stark apparatus was used to remove generated water. Ethyl acetate (50 mL) and 0.5 N HCl (50 mL) were added. Organic phase was separated, washed with saturated aq. NaHCO3, dried over Na2SO4, concentrated in vacuo to give an oil. The oil was dry-packed onto a silica gel column, eluted with hexane first, then with 5% to 10% EtOAc in hexane gradually to give the desired product as a mixture of trans and cis isomers (0.44 g) (yield: 31%).

B. Preparation of N-[4-(2{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]-2-methoxycarbonyl-3-(3-cyanophenyl)-acrylamide.

Compound (2E) and (2Z) tert-butyl 2-methoxycarbonyl-3-(3-cyanophenyl)-acrylate (0.220 g, 0.767 mmol) was dissolved in TFA (6 mL). It was allowed to stand at room temperature for 2 h. TFA was removed in vacuo to give a solid. The solid was dissolved in anhydrous DMF (7 mL). To the solution, 4-(2'-tert-butylaminosulfonylphenyl)aniline (0.242 g, 0.796 mmol) and triethylamine (0.200 mL, 1.44 mmol) were added, followed by addition of BOP (0.416 g, 0.940 mmol). The mixture was then stirred room temperature overnight. Water and ethyl acetate were added. Organic phase was separated, washed with saturated aq. NaHCO3, dried over Na2SO4, concentrated in vacuo to give a solid (0.391 g) (yield: 99%). It was sufficiently pure to be used in the following reaction.

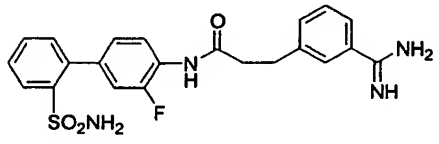
C. Preparation of N-{4-[(2-aminosulfonyl)phenyl]phenyl}-2-methoxycarbonyl-3-(3-amidinophenyl)-acrylamide.

To a solution of compound N-[4-(2{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]-2-methoxycarbonyl-3-(3-cyanophenyl)-acrylamide (0.390 g, 0.750 mmol) in anhydrous MeOH cooled in ice bath, hydrogen chloride gas was bubbled to saturation. The solution was then stirred at room temperature overnight. It was concentrated in vacuo, the residue was dissolved in anhydrous MeOH (6 mL). To the solution, NH4OAc (0.450 g, 5.84 mmol) was added. The mixture was heated to reflux for 0.5 h. It was concentrated in vacuo. The residue was purified by HPLC using a gradient of 5% CH3CN in H2O (containing 0.1% TFA) to 95% CH3CN over 90 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (60 mg) (yield: 17%). MS 479 (M + H)

D. Preparation of N-{4-[(2-aminosulfonyl)phenyl]phenyl}-2-methoxycarbonyl-3-(3-amidinophenyl)-propionamide.

A solution of compound N-{4-[(2-aminosulfonyl)phenyl]phenyl}-2-methoxycarbonyl-3-(3-amidinophenyl)-acrylamide (9 mg, 19 μmol) and Pd-C (10%, 7 mg) in MeOH (2 mL) was hydrogenated under balloon H2 overnight. The solution was then filtered through a plug of celite. The filtrate was concentrated in vacuo to give the titled compound (9 mg) (yield: 99%). MS 481 (M + H)

Example 3. Preparation of N-{4-[(2-aminosulfonyl)phenyl]-2-fluorophenyl}-3-(3-amidinophenyl)-propionamide.



A. Preparation of 4-[(2-tert-butylaminosulfonyl)phenyl]-2-fluoro-aniline.

To a solution of 2-(tert-butylaminosulfonyl)-benzeneboronic acid (2.06g, 8mmol) in toluene (60ml) was added water (4ml), 8N sodium hydroxide (8ml), isopropanol (16ml), 2-fluoro-4-iodoaniline (3.8g, 16mmol) and tetrakis(triphenylphosphine)palladium(0) (464mg, 0.4mmol). The mixture was refluxed for 3-4 hrs, cooled to room temperature, and diluted with ethyl acetate. The organic layer was washed with water (25ml), and dried over magnesium sulfate. After the evaporation of the solvent *in vacuo*, the crude reside was purified by silica gel column chromatography using solvent system 20-30% ethyl acetate in hexane as eluent to give the title compound as a white solid (1.49g, 58%). ES-MS (M+H)+ = 323.

B. Preparation of (2Z)-N-{4-[2-(tert-butylaminosulfonyl)phenyl]-2-fluorophenyl}-3-(3-cyanophenyl)-acrylamide

To a solution of 4-[(2-tert-butylaminosulfonyl)phenyl]-2-fluoro-aniline (161mg, 0.5mmol) in dichloromethane (5ml) was added 2.0M trimethylaluminum in hexane (0.75ml, 1.5mmol). The mixture was stirred at room temperature for 30 minutes, methane gas evolved. A solution of (Z) methyl 3-cyanocinnamate (94mg, 0.5mmol) in dichloromethane (1ml) was added. The mixture was stirred at room temperature overnight. 1N hydrochloride was added to acidify the solution to pH=2. After the addition of water and dichloromethane, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over magnesium sulfate, and concentrated *in vacuo* to give the title compound as a yellow oil (260mg, 100%). ES-MS (M+H)+ = 478.

C. (2Z)-N-{4-[2-(aminosulfonyl)phenyl]-2-fluorophenyl}-3-(3-amidinophenyl)-acrylamide

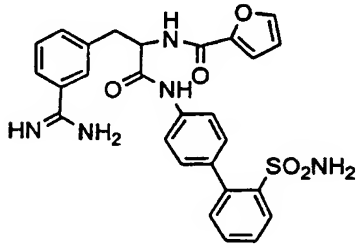
To a solution of (2Z)-N-{4-[2-(tert-butylaminosulfonyl)phenyl]-2-fluorophenyl}-3-(3-cyanophenyl)-acrylamide (100mg, 0.21mmol) in absolute methanol (3ml) in an ice bath was saturated with hydrochloride gas for 10 minutes. The mixture was stirred at room temperature for 3 hrs. After the evaporation of solvent *in vacuo*, the residue was dissolved in absolute methanol (3ml), and ammonia acetate (97mg, 1.26mmol) was added. The mixture was refluxed for 3 hrs. The solvent was evaporated *in vacuo*. The crude residue was purified by RP-HPLC

to give the title compound as a white powder (53mg, 58%). ES-MS (M+H)+ = 439.

D. Preparation of N-{4-[(2-aminosulfonyl)phenyl]-2-fluorophenyl}-3-(3-amidinophenyl)-propionamide.

To a solution of (2Z)-N-{4-[2-(aminosulfonyl)phenyl]-2-fluorophenyl}-3-(3-amidinophenyl)-acrylamide (30mg, 0.07mmol) in absolute methanol (2ml) was added 10% Pd/C (catalytic amount). The mixture was hydrogenated under balloon for 1hr. After the filtration through celite, the solvent was evaporated *in vacuo*. The residue was purified by RP-HPLC to give the compound as a white powder (25mg, 81%). ES-MS (M+H)+ = 441.

Example 4. Preparation of N-{4-[(2-aminosulfonyl)phenyl]phenyl}-2-(2-furylcarbonylamino)-3-(3-amidinophenyl)-propionamide



A. Preparation of 3-[2-(furyl-2-yl)-5-oxo-1,3-oxazolin-4-ylidene)methyl]benzenecarbonitrile.

A mixture of 3-cyanobenzaldehyde (2.102g, 15.320mmol), N-2-furoylglycine (1.85g, 10.9 mmol), and sodium acetate (0.636g, 7.753mmol) in 15ml acetic anhydride was refluxed for 7 hours. The mixture was then cooled to room temperature before cooling in the freezer over night. The solid was washed with ice cold water then filtered (0.472g, 1.788mmol, 16%). ES-MS(M+H)+=265.

B. Preparation of N-{4-[(2-tert-butylaminosulfonyl)phenyl]phenyl}-2-(2-furylcarbonylamino)-3-(3-cyanophenyl)-acrylamide.

To a solution of 4-[(2-tert-butylaminosulfonyl)phenyl]-aniline (0.152g, 0.500mmol) in 9ml DCM was added trimethylaluminum (1ml, 2M solution in hexanes, 2mmol) which was allowed to stir for ½ hour. Then 3-[(2-(2-furyl)-5-oxo-1,3-oxazolin-4-ylidene)methyl]benzenecarbonitrile (0.11g, 0.417mmol) was added drop wise as a solution in 3ml DCM. Three hours later 6M HCl was added drop wise to pH=0. 10ml portions of water and DCM were also added and the aqueous layer was extracted twice with 10ml portions of DCM. The organic layers were dried over MgSO4, filtered and concentrated in vacuo to yield the desired product (0.259, 0.456, 109%). ES-MS(M+H)+=569.

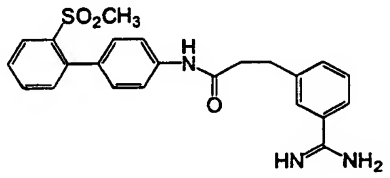
C. Preparation of N-{4-[(2-tert-butylaminosulfonyl)phenyl]phenyl}-2-(2-furylcarbonylamino)-3-(3-amidinophenyl)-propionamide.

To a solution of N-{4-[(2-tert-butylaminosulfonyl)phenyl]phenyl}-2-(2-furylcarbonylamino)-3-(3-cyanophenyl)-acrylamide (0.259g, 0.456mmol) in 7ml ethanol was added hydroxyamine (0.192g, 2.763mmol) and triethyl amine (0.762ml, 5.407mmol). This mixture was refluxed for 2 hours before it was concentrated in vacuo. The residue was dissolved in AcOH (5ml), then acetic anhydride (0.30ml, 3.182mmol) was added and the mixture was allowed to stir for1.5 hours. The mixture was concentrated in vacuo. The residue was dissolved in dry MeOH (3ml), 5%Pd/C (22.7mg) was added. A balloon filled with hydrogen gas was fitted to the flask with an adapter. The flask was evacuated and backfilled with hydrogen gas three times before being run for 0.75 hour. The mixture was then filtered over a bed of celite and concentrated in vacuo. The residue was purified via Preparative HPLC to yield the desired product (0.075g, 0.128mmol, 28%). ES-MS(M+H)+=588.

D. Preparation of N-{4-[(2-aminosulfonyl)phenyl]phenyl}-2-(2-furylcarbonylamino)-3-(3-amidinophenyl)-propionamide

A solution of compound N-{4-[(2-tert-butylaminosulfonyl)phenyl]phenyl}-2-(2-furylcarbonylamino)-3-(3-amidinophenyl)-propionamide (0.075g, 0.128mmol) in TFA (6ml) was stirred at room temperature for 2 hours. The mixture was concentrated in vacuo and the residue was purified via preparative HPLC to give the product (0.040g, yield: 58%). ES-MS(M+H)+=532.

Example 5. Preparation of N-[4-(2-methylsulfonylphenyl)phenyl]-3-(3-amidinophenyl)-propionamide.



A. Preparation of N-{4-[(2-methylsulfonyl)phenyl]phenyl}-3-(3-cyanophenyl)-acrylamide

To a solution of 4-(2-methylsulfonylphenyl)aniline (74.1 mg, 0.3 mmol, 1.0 equiv) in 5 mL of CH_2Cl_2 at 0°C, was added a solution of $AlMe_3$ (2M in hexanes, 0.7 mL, 5 equiv). After 15min, methyl 3-cyanocinnamate (56.1 mg, 1.0 equiv) was added. The resulting solution was stirred overnight, carefully quenched with water, diluted with ethyl acetate. The organic layer was dried, evaporated and chromatographied on silica gel to give the product in 55% yield. LRMS found for $C_{23}H_{19}N_2O_3S$ $(M+H)^+$: 403.1.

B. Preparation of N-{4-[(2-methylsulfonyl)phenyl]phenyl}-3-(3-amidinophenyl)-acrylamide

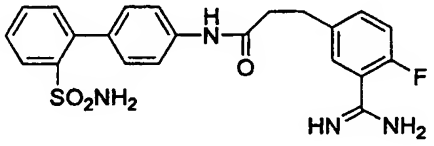
The compound N-{4-[(2-methylsulfonyl)phenyl]phenyl}-3-(3-cyanophenyl)-acrylamide (25 mg) was dissolved in 5 mL of methanol . The reaction mixture was cooled to 0°C and HCl gas was bubbled in until saturation. The mixture was stirred at room temperature overnight. The solvent was evaporated and the resulting residue was treated with ammonium acetate and 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude pruduct was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give the desired compound in 77% yield. LRMS found for $C_{23}H_{22}N_3O_3S$ $(M+H)^+$: 420.1.

C. Preparation of N-[4-(2-methylsulfonylphenyl)phenyl]-3-(3-amidinophenyl)-propionamide

The compound N-{4-[(2-methylsulfonyl)phenyl]phenyl}-3-(3-amidinophenyl)-acrylamide (8 mg) and 5 mg of 10% Pd/C was suspended in 1 mL of methanol . The reaction mixture was stirred under 1atm hydrogen balloon for 2h and filtered. The solvent was removed at reduced pressure and the crude product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to

give the desired compound in 63% yield. LRMS found for $C_{23}H_{24}N_3O_3S$ $(M+H)^+$: 422.1.

Example 6. Preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-(3-amidino-4-fluorophenyl)-propionamide.



A. Preparation of 2-fluoro-5-bromomethylbenzonitrile.

2-Fluoro-5-methyl benzonitrile (1.26g, 9.32 mmol) was mixed with NBS (1.66 g, 9.32 mmol), benzoyl peroxide (79 mg, 0.33 mmol) in CCl_4 (45mL). The mixture was refluxed for 2.5 hrs. It was cooled to room temperature, filtered and concentrated *in vacuo* to give the title compound. ES-MS (M+H)+ = 213.1.

B. Preparation of 3-cyano-4-fluorobenzaldehyde.

To a solution of 2-fluoro-5-bromomethylbenzonitrile (9.32 mmol) in $CHCl_3$ (50 mL), was added trimethylamino N-oxide (1.7 g, 23.3 mmol). The mixture was refluxed for 3 hrs. Water was added. The organic layer was dried over $MgSO_4$, filtered and filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography using solvent system 20% EtOAc in hexane as eluant to give the title compound. ES-MS (M+H)+ = 150.1.

C. Preparation of (Z) methyl 3-cyano-4-fluorocinnamate

To a solution of bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl) phosphonate (0.12 mL, 0.58 mmol) and 18-crown-6 (770 mg, 2.92 mmol) in THF (5 mL) at –78°C, was added potassium bis(trimethylsilyl)amide (1.17 mL, 0.57 mmol) dropwise. After the addition was complete, 3-cyano-4-fluorobenzaldehyde (87 mg, 0.58 mmol) in THF (2 mL) was added. The mixture was stirred at –78°C for 1 hour. Aqueous NH_4Cl solution was added to quench the reaction. Water and EtOAc was added to the mixture. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. This was purified by silica gel column chromatography using

solvent system 20% EtOAc in hexane as eluant to give the title compound (85 mg, 71%). ES-MS (M+H)+ = 206.1.

D. Preparation of (2Z)-N-[4-(2-[(tert-butylamino)sulfonyl]phenyl)phenyl]-3-(3-cyano-4-fluorophenyl)-acrylamide

To a solution of 4-[(2-tert-butylaminosulfonyl)phenyl]-aniline (121.6 mg, 0.4 mmol) in DCM (3 mL) was added trimethylaluminum (0.6 mL, 2M in hexane) dropwise. The reaction mixture was stirred at room temperature for 30 min. Compound (Z) methyl 3-cyano-4-fluorocinnamate (82 mg, 0.4 mmol) in DCM (2 mL) was added dropwise. The mixture was stirred at room temperature overnight. 2N HCl was added to pH 2. Water and DCM were added. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. It was purified by silica gel column chromatography using solvent system 50% EtOAc in hexane as eluant to give the title compound. ES-MS (M+Na)+ = 500.1.

E. Preparation of (2Z)-N-{4-[(2-aminosulfonyl)phenyl]phenyl}-3-(3-amidino-4-fluorophenyl)-acrylamide

A solution of (2Z)-N-[4-(2-[(tert-butylamino)sulfonyl]phenyl)phenyl]-3-(3-cyano-4-fluorophenyl)-acrylamide (99 mg, 0.208 mmol) in MeOH (10 mL) was treated with a stream of HCl gas for 10 min. at 0°C. The resulting solution was capped, stirred at room temperature overnight and evaporated *in vacuo*. The residue was reconstituted in MeOH (10 mL) and the mixture was treated with NH_4OAc (80 mg, 1.04 mmol). The reaction mixture was refluxed for 2 hrs. and concentrated *in vacuo*. The obtained residue was purified by RP-HPLC to give the title compound as a white powder. ES-MS (M+H)+ = 439.1.

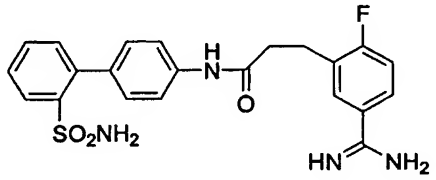
F. Preparation of N-{4-[(2-aminosulfonyl)phenyl]phenyl}-3-(3-amidino-4-fluorophenyl)-propionamide

The compound (2Z)-N-{4-[(2-aminosulfonyl)phenyl]phenyl}-3-(3-amidino-4-fluorophenyl)-acrylamide (10 mg, 0.022 mmol) was dissolved in MeOH (5 mL) and 10% Pd/C (catalytic amount) was added. The mixture was hydrogenated under balloon overnight, filtered through Celite to remove the catalyst and the filtrate was

evaporated. The obtained residue was purified by RP-HPLC to give the title compound as a white powder. ES-MS (M+H)+ = 441.1.

Example 7. Preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-(2-fluoro-5-amidinophenyl)-propionamide.

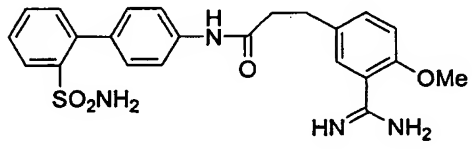
A. Preparation of 2-fluoro-5-cyanobenzaldehyde.



To a solution of LDA (2.6 mL, 2N solution in hexane, 5.2 mmol) in THF (10 mL) at –78°C, was added 4-fluorobenzonitrile in THF (10 mL) dropwise. The mixture was stirred at –78°C for 1 hour. To the mixture was added DMF (0.4 mL). The mixture was stirred at –78°C for another 15 min., quenched rapidly with AcOH (2 mL) and water (10 mL), extracted with ether (50 mL). The ether extracts were washed with 1N HCl (10 mL), brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the title compound. (M+H)+ = 150.

B. Preparation of the final compound N-[4-(2-aminosulfonylphenyl)phenyl]-3-(2-fluoro-5-amidinophenyl)-propionamide, starting from 2-fluoro-5-cyanobenzaldehyde, was completed analogously to preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-(3-amidino-4-fluorophenyl)-propionamide in Example 6. ES-MS (M+H)+ = 441.1.

Example 8. Preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-(3-amidino-4-methoxyphenyl)-propionamide.



A. Preparation of 3-cyano-4-methoxybenzyl alcohol.

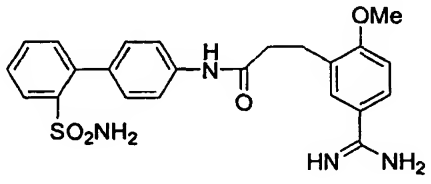
To a solution of methyl-3-cyano-4-methoxybenzoate (5g, 26.2 mmol) in THF (50 mL) was added lithium borohydride (53 mL, 2.00M solution in THF, 105 mmol) at room temperature. The mixture was stirred at room temperature overnight. 1N HCl was slowly added until bubbling stopped. THF was removed *in vacuo* and EtOAc and water were added. The organic layer was washed with water, saturated $NaHCO_3$ solution, brine, dried with Na_2SO_4 and solvent evaporated *in vacuo* to give the title compound (3.7 g, 86.7%).

B. Preparation of 3-cyano-4-methoxybenzaldehyde.

To a solution of 3-cyano-4-methoxybenzyl alcohol (2g, 12.3 mmol) in DMSO (50 mL) was added IBX (4.673g, 17.7 mmol) slowly. The mixture was stirred at room temperature overnight. EtOAc and water were added. The formed precipitate was removed. The organic layer was washed with 1N HCl, water, saturated $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The obtained residue was purified by silica gel column chromatography using DCM as eluant to give the title compound (1.1g, 56%). ES-MS (M+H)+ = 162.1.

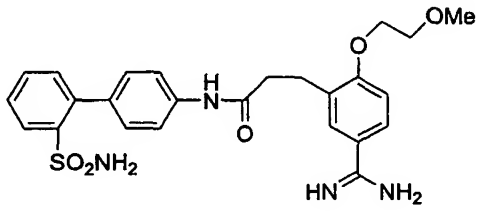
C. Preparation of the final compound N-[4-(2-aminosulfonylphenyl)phenyl]-3-(3-amidino-4-methoxyphenyl)-propionamide, starting from 3-cyano-4-methoxybenzaldehyde, was completed analogously to preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-(3-amidino-4-fluorophenyl)-propionamide in Example 6. ES-MS (M+H)+ = 443.1.

Example 9. Preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-(2-methoxy-5-amidinophenyl)-propionamide.



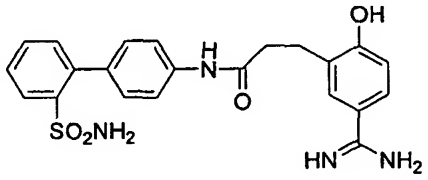
The compound was prepared analogously to preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-(3-amidino-4-methoxyphenyl)-propionamide in Example 8. ES-MS (M+H)+ = 443.1.

Example 10. Preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-(2-(2-methoxyethoxy)-5-amidinophenyl)-propionamide.

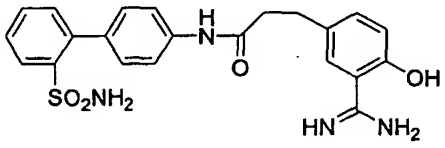


The compound was prepared analogously to preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-(3-amidino-4-methoxyphenyl)-propionamide in Example 8. ES-MS (M+H)+ = 487.1.

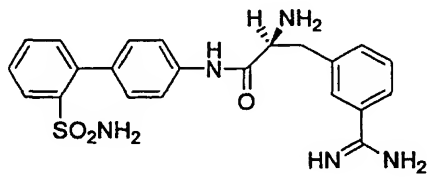
Example 11. Preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-(2-hydroxy-5-amidinophenyl)-propionamide. MS (M+H)+ = 429.



Example 12. Preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-(4-hydroxy-3-amidinophenyl)-propionamide. MS (M+H)+ = 429.



Example 13. Preparation of (2S) N-[4-(2-aminosulfonylphenyl)phenyl]-2-amino-3-(3-amidinophenyl)-propionamide.



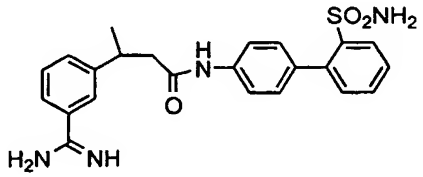
A. Preparation of (2S) N-[4-(2-(tert-butylaminosulfonyl)phenyl)phenyl]-2-tert-butoxycarbonylamino-3-(3-cyanophenyl)-propionamide

N-Boc-meta-cyano-phenylalanine (200 mg, 0.69 mmol) and 4-[(2-tert-butylaminosulfonyl)phenyl]-aniline (210 mg, 0.69 mmol) were dissolved in DMF (3 mL). DIEA (0.24 mL, 1.4 mmol) was added followed by the addition of the coupling reagent PyBOP (572 mg, 1.1 mmol). The solution was stirred at room temperature for 12 hours. The reaction mixture was diluted in a mixture of EtOAc/H_2O. The organic layer was washed with water, saturated Na_2CO_3, water, 1M $KHSO_4$, brine, dried over $MgSO_4$, filtered and solvent evaporated to give the title compound. ES-MS (M+H)+ = 521.1.

B. Preparation of (2S) N-[4-(2-aminosulfonylphenyl)phenyl]-2-amino-3-(3-amidinophenyl)-propionamide.

A solution of (2S) N-[4-(2-(tert-butylaminosulfonyl)phenyl)phenyl]-2-tert-butoxycarbonylamino-3-(3-cyanophenyl)-propionamide (132 mg, 0.23 mmol) in MeOH (10 mL) was treated with a stream of HCl gas for 10 min. at 0°C. The resulting solution was capped, stirred at room temperature overnight and evaporated *in vacuo*. The residue was reconstituted in MeOH (10 mL) and the mixture was treated with NH_4OAc (540 mg, 7 mmol). The reaction mixture was refluxed for 2 hrs. and concentrated *in vacuo*. The obtained residue was purified by RP-HPLC to give the title compound as a white powder. ES-MS (M+H)+ = 438.1.

Example 14. Preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-methyl-3-(3-amidinophenyl)-propionamide.



Part A. Ethyl 3-{[(trifluoromethyl)sulfonyl]-oxy}-2-propenoate and ethyl (Z)-3-{[(trifluoromethyl)-sulfonyl]oxy}-2-propenoate

To a solution of ethyl acetoacetate (1.3g, 10mmol) in 10ml anhydrous dichloromethane was added triethylamine (1.46ml, 10.5mmol). The reaction was cooled to –78°C under argon to which trifluoromethanesulfonic anhydride (2.96g, 10.5mmol) was added dropwise via syringe over 5 minutes. Reaction was allowed to warm to room temperature and stirred over night. Next morning the reaction was diluted with 25ml dichloromethane, organic was washed with 2x50ml water, 2x50ml 1N HCl, dried over magnesium sulfate, filtered and concentrated. Crude oil was chromatographed on silica gel using 5% EtOAc in hexane as the eluent to give 1) ethyl (E)-3-{[(trifluoromethyl)sulfonyl]-oxy}-2-propenoate (800mg, 60%) as a clear oil: H^1NMR ($CDCl_3$) : 1.247-1.282 (t, 3H); 2.471 (s, H); 4.155-4.209 (m, 2H); 5.912 (s, H); and 2) ethyl (Z)-3-{[(trifluoromethyl)sulfonyl]-oxy}-2-propenoate (450mg, 30%) as a clear oil: H^1NMR ($CDCl_3$) : 1.247-1.283 (t, 3H); 2.131 (s, 3H); 4.18-4.233 (m, 2H); 5.736 (s, H)

Part B. Ethyl (Z) 3-(3-cyanophenyl)-2-propenoate

To a solution of ethyl (Z)-3-{[(trifluoromethyl)sulfonyl]-oxy}-2-propenoate (330mg, 1.25mmol) in 5ml anhydrous dioxane was added potassium phosphate (398mg, 1.88mmol), 3-cyanophenyl boronic acid (185mg, 1.25mmol), and tetrakis (triphenylphosphine)palladium(0) (36mg, 0.031mmol). Reaction mixture was heated to reflux and stirred overnight. Mixture was filtered through a pad of Celite, diluted with 50ml ethyl acetate, washed with 2x50ml water, 2x50ml saturated brine solution, dried over magnesium sulfate, filtered and concentrated in vacuo. Residue was chromatographed on silica gel using 5% EtOAc in hexane as the eluent to give ethyl

(Z) 3-(3-cyanophenyl)-2-propenoate (240mg, 71%) as a clear oil after drying. ES-MS ($M+H^+$): 216.05

Part C. Preparation of (2Z) N-[4-(2-aminosulfonylphenyl)phenyl]-3-methyl-3-(3-amidinophenyl)-acrylamide.

To a solution of 2'-tert-butylaminosulfonyl-4-amino-[1,1']-biphenyl (198mg, 0.65mmol) in 5ml anhydrous dichloromethane was added a solution of 2M trimethylaluminum in hexane (0.98ml, 1.95mmol). Reaction was stirred at room temperature for 20 minutes to which a solution of ethyl (Z) 3-(3-cyanophenyl)-2-propenoate (140mg, 0.65mmol) in 1ml anhydrous dichloromethane was added. Reaction was stirred at room temperature overnight. Reaction was quenched with 5ml 1N HCl after which an additional 20ml dichloromethane was added. Organic was washed with 2x25ml water, dried over magnesium sulfate and concentrated to give (2Z) N-[4-(2-tert-butylaminosulfonylphenyl)phenyl]-3-methyl-3-(3-cyanophenyl)-acrylamide (200mg, 65%) as a light brown residue which was sufficiently pure to be used without further purification.

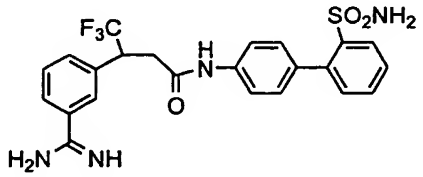
To a solution of (2Z) N-[4-(2-tert-butylaminosulfonylphenyl)phenyl]-3-methyl-3-(3-cyanophenyl)-acrylamide (90mg, 0.19mmol) in 5ml anhydrous methanol cooled in an ice bath was bubbled HCl gas until saturation was achieved. Reaction was allowed to warm to room temperature and stirred overnight. The reaction was then concentrated in vacuo and dried under hi vacuum. The dried residue was dissolved in 5ml anhydrous methanol to which ammonium acetate (144mg, 2mmol) was added and the reaction heated to reflux for 2 hours. The reaction was concentrated and purified on a 2x25cm Vydac C_{18} HPLC column to give 3-((1Z)-1-methyl-2-{N-[4-(2-sulfamoylphenyl)phenyl]carbamoyl}vinyl)-benzenecarboxamidine (35mg, 20%) as a fluffy white powder after lyophilization. ES-MS ($M+H^+$): 435.1

Part D. Preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-methyl-3-(3-amidinophenyl)-propionamide

To a solution of (2Z) N-[4-(2-aminosulfonylphenyl)phenyl]-3-methyl-3-(3-amidinophenyl)-acrylamide (5mg, 0.0115mmol) in 4ml methanol was added 10% Pd on carbon (2mg). Mixture was treated with 50psi hydrogen on the PARR apparatus

for 1hr. Reaction was filtered through a pad of Celite, concentrated and lyophilized to give the title compound (3mg, 60%) as a fluffy white powder. ES-MS ($M+H^+$): 437.1

Example 15. Preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-trifluoromethyl-3-(3-amidinophenyl)-propionamide.



Part A. Ethyl (Z)-4,4,4-trifluoro-3-{[(trifluoromethyl)sulfonyl]-oxy}-2-butenoate

To a solution of ethyl trifluoroacetoacetate (5g, 27.2mmol) in 20ml anhydrous dichloromethane was added triethylamine (5.7ml, 40.7mmol). Reaction was cooled under argon to –78°C to which trifluoromethanesulfonic anhydride (11.5g, 10.5mmol) was added dropwise via syringe over 5 minutes. Reaction was allowed to warm to room temperature and stirred over night. Next morning the reaction was diluted with 25ml dichloromethane, organic was washed with 2x50ml water, 2x50ml 1N HCl, dried over magnesium sulfate, filtered and concentrated in vacuo. Crude oil was chromatographed on silica gel using 5% EtOAc in hexane as the eluent to give ethyl (Z)-4,4,4-trifluoro-3-{[(trifluoromethyl)sulfonyl]-oxy}-2-butenoate (7.7g, 90%) as a clear light yellow oil after drying. H^1NMR ($CDCl_3$) : 1.31-1.35 (t, 3H); 4.33-4.35 (m, 2H); 6.535 (s, H).

Part B. Ethyl (2E)-3-(3-cyanophenyl)-4,4,4-trifluorobut-2-enoate

To a solution of ethyl (Z)-4,4,4-trifluoro-3-{[(trifluoromethyl)sulfonyl]-oxy}-2-butenoate (250mg, 0.79mmol) in 5ml anhydrous dioxane was added potassium phosphate (251mg, 1.19mmol), 3-cyanophenyl boronic acid (116mg, 0.79mmol), and tetrakis (triphenylphosphine)palladium(0) (23mg, 0.02mmol). Reaction mixture was heated to reflux and stirred overnight. Mixture was filtered through a pad of Celite, diluted with 50ml ethyl acetate, washed with 2x50ml water, 2x50ml saturated brine solution, dried over magnesium sulfate, filtered and concentrated in vacuo. Residue was chromatographed on silica gel using 20% EtOAc in hexane as the eluent to give

ethyl (2E)-3-(3-cyanophenyl)-4,4,4-trifluorobut-2-enoate (150mg, 79%) as a yellow residue after drying. H^1NMR ($CDCl_3$) 1.107-1.142 (t, 3H); 4.05-4.107 (m, 2H); 6.684 (s, H); 7.38-7.72 (m, 4H).

Part C. Preparation of (2E) N-[4-(2-aminosulfonylphenyl)phenyl]-3-trifluoromethyl-3-(3-amidinophenyl)-acrylamide.

To a solution of 2'-tert-butylaminosulfonyl-4-amino-[1,1']-biphenyl (79mg, 0.26mmol) in 5ml anhydrous dichloromethane was added a solution of 2M trimethylaluminum in hexane (0.39ml, 0.78mmol). Reaction was stirred at room temperature for 20 minutes to which a solution of ethyl (Z) 3-(3-cyanophenyl)-4,4,4-trifluoro-2-butenoate (70mg, 0.26mmol) in 1ml anhydrous dichloromethane was added. Reaction was stirred at room temperature overnight. Reaction was quenched with 5ml 1N HCl after which an additional 20ml dichloromethane was added. Organic was washed with 2x25ml water, dried over magnesium sulfate, filtered and concentrated to give (2E) N-[4-(2-tert-butylaminosulfonylphenyl)phenyl]-3-trifluoromethyl-3-(3-cyanophenyl)-acrylamide (120mg, 88%) as a yellow foam which was sufficiently pure to be used without further purification.

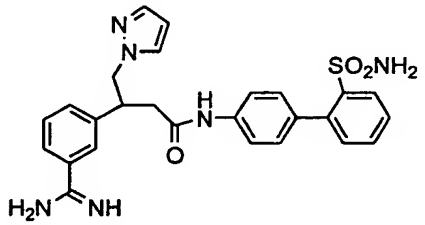
To a solution of (2E) N-[4-(2-tert-butylaminosulfonylphenyl)phenyl]-3-trifluoromethyl-3-(3-cyanophenyl)-acrylamide (90mg, 0.19mmol) in 10ml 1:1 ethyl acetate:anhydrous methanol cooled to –78°C was bubbled HCl gas until saturation was achieved. Reaction was placed in the refrigerator at 0°C over the weekend. The reaction was then concentrated in vacuo and dried under hi vacuum. The dried methyl imidate residue was dissolved in 5ml anhydrous methanol to which ammonium acetate (144mg, 2mmol) was added and the reaction heated to reflux for 2 hours. The reaction was concentrated then treated with 10ml trifluoroacetic acid for 2hrs, concentrated and purified on a 2x25cm Vydac C_{18} HPLC column to give the title compound (57mg, 47%) as a fluffy white powder after lyophilization. ES-MS ($M+H^+$): 489.15

Part D. Preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-trifluoromethyl-3-(3-amidinophenyl)-propionamide

To a solution of (2E) N-[4-(2-aminosulfonylphenyl)phenyl]-3-trifluoromethyl-3-(3-amidinophenyl)-acrylamide (10mg, 0.02mmol) in 4ml methanol was added 10% Pd on carbon (2mg). Mixture was treated with hydrogen at 1 atmosphere under

balloon for 1hr. Reaction was filtered through a pad of Celite, concentrated and lyophilized to give the title compound (8mg, 82%) as a fluffy white powder. ES-MS ($M+H^+$): 491.1

Example 16. Preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-(1-pyrazolylmethyl)-3-(3-amidinophenyl)-propionamide.



Part A. 3-(2-bromoacetyl) benzonitrile

To a solution of 3-acetobenzonitrile (5g, 0.0344mol) in 45ml glacial acetic acid was added pyridinium tribromide (11.3g, 0.0355mol). Reaction was stirred at room temperature under argon overnight. Reaction was then quenched with a saturated sodium sulfite solution (20ml) and extracted with 3x25ml dichloromethane. Combined organic phases were washed with 2x25ml water, dried over magnesium sulfate, filtered and concentrated in vacuo. Crude oil was chromatographed on silica gel using 5% EtOAc in hexane as the eluent to give 3-(2-bromoacetyl) benzonitrile (4.5g, 58%) as a white solid. H^1NMR ($CDCl_3$) 4.371-4.403 (s, 2H); 7.613-7.664 (m, H); 7.838-7.888 (m, H); 8.192-8.261 (m, 2H)

Part B. 3-[2-(*1H*-1-Pyrazolyl)acetyl]benzonitrile

To a solution of 3-(2-bromoacetyl)benzonitrile (500mg, 2.23mmol) in 5ml dichloromethane was added pyrazole (304mg, 4.46mmol) and triethylamine (0.31ml, 2.23mmol). Reaction was stirred at room temperature over night. Reaction was then diluted with 20ml dichloromethane, washed with 2x25ml water, 2x25ml 1N HCl, dried over magnesium sulfate, filtered and concentrated in vacuo. Crude residue was chromatographed on silica gel using 2.5% EtOAc in hexane to give 3-[2-(*1H*-1-

pyrazolyl)acetyl]benzonitrile (330mg, 70%) as a clear oil after drying. ES-MS ($M+H^+$): 212.05

Part C. Methyl (E)-3-(3-cyanophenyl)-4-(*1H*-1-pyrazolyl)-2-butenoate

To a solution of bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate (0.39ml, 1.87mmol) in 5ml anhydrous tetrahydrofuran was added a solution of 18-crown-6 (2g, 7.8mmol) in 5ml anhydrous tetrahydrofuran. Reaction was cooled to –78° C to which a 0.5M solution of potassium bis(trimethylsilyl)amide in toluene (0.93ml, 1.87mmol) was added all at once. The reaction mixture was stirred at –78° C for 20 minutes after which a solution of 3-[2-(*1H*-1-pyrazolyl)acetyl]- benzonitrile (330mg, 1.56mmol) in 5ml anhydrous tetrahydrofuran was added dropwise over several minutes. Reaction was gradually allowed to warm to room temperature and stirred for 5 hours. Reaction was then quenched with a saturated ammonium chloride solution (10ml) and extracted with 2x25ml diethyl ether. Combined organic layers were washed with 2x25ml water, 2x25ml saturated brine solution, dried over magnesium sulfate, filtered and concentrated to a brown residue. Crude residue was chromatographed on silica gel using a gradient of 5% EtOAc in hexane containing 0.1% triethylamine to 20% EtOAc in hexane containing 0.1% triethylamine to give methyl (E)-3-(3-cyanophenyl)-4-(*1H*-1-pyrazolyl)-2-butenoate (135mg, 32%) as a clear oil after drying. H^1NMR ($CDCl_3$) 3.521 (s, #H); 4.98 (s, 2H); 5.694 (s, H); 6.237-6.247 (t, H); 7.296-7.593 (m, 6H). NOE experiment confirmed the stereochemical configuration.

Part D. Preparation of (2E) N-[4-(2-aminosulfonylphenyl)phenyl]-3-trifluoromethyl-3-(3-amidinophenyl)-acrylamide.

To a solution of 2'-tert-butylaminosulfonyl-4-amino-[1,1']-biphenyl (105mg, 0.34mmol) in 4ml anhydrous dichloromethane was added a solution of 2M trimethylaluminum in hexane (0.5ml, 1.02mmol). Reaction was stirred at room temperature for 20 minutes to which a solution of methyl (E)-3-(3-cyanophenyl)-4-(1*H*-1-pyrazolyl)-2-butenoate (90mg, 0.34mmol) in 1ml anhydrous dichloromethane was added. Reaction was stirred at room temperature overnight. Reaction was quenched with 5ml 1N HCl after which an additional 20ml dichloromethane was added. Organic was washed with 2x20ml water, dried over magnesium sulfate, filtered and concentrated to give (2E) N-[4-(2-tert-butylaminosulfonylphenyl)phenyl]-3-(1-

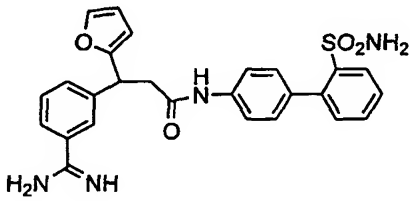
pyrazolylmethyl)-3-(3-cyanophenyl)-acrylamide (155mg, 85%) as an off-white foam which was sufficiently pure to be used without further purification.

To a solution of (2E) N-[4-(2-tert-butylaminosulfonylphenyl)phenyl]-3-(1-pyrazolylmethyl)-3-(3-cyanophenyl)-acrylamide (155mg, 0.287mmol) in 10ml 1:1 ethyl acetate:anhydrous methanol cooled to –78°C was bubbled HCl gas until saturation was achieved. Reaction was allowed to warm to room temperature and stirred overnight. The reaction was then concentrated in vacuo and dried under hi vacuum. The dried methyl imidate residue was dissolved in 5ml anhydrous methanol to which ammonium acetate (77mg, 1mmol) was added and the reaction heated to reflux for 2 hours. The reaction was concentrated, treated with trifluoroacetic acid (10ml) for 2hrs, concentrated and purified on a 2x25cm Vydac C_{18} HPLC column to give the title compound (40mg, 28%) as a fluffy white powder after lyophilization. ES-MS ($M+H^+$): 501.1

Part E. N-[4-(2-aminosulfonylphenyl)phenyl]-3-(1-pyrazolylmethyl)-3-(3-amidinophenyl)-propionamide.

To a solution of (2E) N-[4-(2-aminosulfonylphenyl)phenyl]-3-trifluoromethyl-3-(3-amidinophenyl)-acrylamide (5mg, 0.01mmol) in 4ml methanol was added 10% Pd on carbon (1mg). Mixture was treated with hydrogen at 1 atmosphere under balloon for 1hr. Reaction was filtered through a pad of Celite, concentrated and lyophilized to give the title compound (5mg, 100%) as a fluffy white powder. ES-MS ($M+H^+$): 503.1

Example 17. Preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-(2-furyl)-3-(3-amidinophenyl)-propionamide.



Part A. Ethyl (Z)-3-(2-furyl)-3-{[(trifluoromethyl)sulfonyl]-oxy}-2-propenoate

To a solution of ethyl *B*-oxo-3-furanpropionate (1g, 5.49mmol) in 5ml anhydrous dichloromethane was added triethylamine (0.847ml, 6.04mmol). Reaction was cooled under argon to –78°C to which trifluoromethanesulfonic anhydride (1.02ml, 6.04mmol) was added dropwise via syringe over 5 minutes. Reaction was allowed to warm to room temperature and stirred over night. Next morning the reaction was diluted with 25ml dichloromethane, organic was washed with 2x50ml water, 2x50ml 1N HCl, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude oil was chromatographed on silica gel using 20% EtOAc in hexane as the eluent to give ethyl (Z)-3-(2-furyl)-3-{[(trifluoromethyl)sulfonyl]-oxy}-2-propenoate (1.6g, 93%) as a light brown solid after drying. H^1NMR ($CDCl_3$) 1.31-1.35 (t, 3H); 4.26-4.314 (m, 2H); 6.065 (s, H); 6.522 (s, H); 7.47 (s, H); 7.76 (s, H).

Part B. Ethyl (E) 3-(3-cyanophenyl)-3-(2-furyl)-2-propenoate

To a solution of ethyl (Z)-3-(2-furyl)-3-{[(trifluoromethyl)sulfonyl]-oxy}-2-propenoate (500mg, 1.59mmol) in 7ml anhydrous dioxane was added potassium phosphate (506mg, 2.4mmol), 3-cyanophenyl boronic acid (234mg, 1.59mmol), and tetrakis (triphenylphosphine)palladium(0) (46mg, 0.04mmol). Reaction mixture was heated to reflux and stirred overnight. Mixture was filtered through a pad of Celite, diluted with 50ml ethyl acetate, washed with 2x50ml water, 2x50ml saturated brine solution, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude residue was chromatographed on silica gel using a gradient from 5% EtOAc in hexane to 10% EtOAc in hexane as the eluent to give ethyl (E) 3-(3-cyanophenyl)-3-(2-furyl)-2-propenoate (100mg, 24%) as a clear yellow oil after drying. H^1NMR ($CDCl_3$) 1.1-1.14 (t, 3H); 4,016-4.035 (m, 2H); 5.293 (s, H); 7.45-7.549 (m, 3H); 7.669 (m, H). ES-MS ($M+H^+$): 268.05

Part C. (2E) N-[4-(2-aminosulfonylphenyl)phenyl]-3-(2-furyl)-3-(3-amidinophenyl)-acrylamide.

To a solution of 2'-*t*Butylaminosulfonyl-4-amino-[1,1']-biphenyl (102mg, 0.336mmol) in 4ml anhydrous dichloromethane was added a solution of 2M trimethylaluminum in hexane (0.5ml, 1.0mmol). Reaction was stirred at room temperature for 20 minutes to which a solution of ethyl (E) 3-(3-cyanophenyl)-3-(2-furyl)-2-propenoate (90mg, 0.336mmol) in 1ml anhydrous dichloromethane was added. Reaction was stirred at room temperature overnight. Reaction was quenched with 5ml

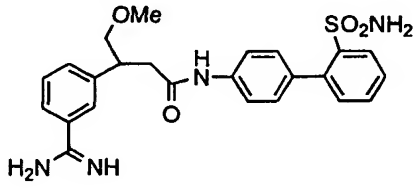
1N HCl after which an additional 20ml dichloromethane was added. Organic was washed with 2x20ml water, dried over magnesium sulfate and concentrated to give (2E)-N-[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]-3-(3-cyanophenyl)-3-(2-furyl)prop-2-enamide (200mg, 112%) as a brown foam which was sufficiently pure to be used without further purification.

To a solution of (2E)-N-[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]-3-(3-cyanophenyl)-3-(2-furyl)prop-2-enamide (176mg, 0.336mmol) in 10ml 1:1 ethyl acetate:anhydrous methanol cooled to –78°C was bubbled HCl gas until saturation was achieved. Reaction was allowed to warm to room temperature and stirred overnight. The reaction was then concentrated in vacuo and dried under hi vacuum. The dried methyl imidate residue was dissolved in 5ml anhydrous methanol to which ammonium acetate (144mg, 2mmol) was added and the reaction heated to reflux for 2 hours. The reaction was concentrated, treated with trifluoroacetic acid (10ml) for 2hrs, concentrated and purified on a 2x25cm Vydac C_{18} HPLC column to give the title compound (60mg, (37%) as a fluffy off-white powder after lyophilization. ES-MS ($M+H^+$): 487.15

Part D. N-[4-(2-aminosulfonylphenyl)phenyl]-3-(2-furyl)-3-(3-amidinophenyl)-propionamide.

To a solution of (2E) N-[4-(2-aminosulfonylphenyl)phenyl]-3-(2-furyl)-3-(3-amidinophenyl)-acrylamide (10mg, 0.02mmol) in 4ml methanol was added 10% Pd on carbon (2mg). Mixture was treated with hydrogen at 1 atmosphere under balloon for 1hr. Reaction was filtered through a pad of Celite, concentrated and lyophilized to give the title compound (9mg, 90%) as a fluffy white powder. ES-MS ($M+H^+$): 489.15

Example 18. Preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-methoxymethyl-3-(3-amidinophenyl)-propionamide.



Part A. Methyl (Z)-4-methoxy-3-{[(trifluoromethyl)sulfonyl]-oxy}-2-butenoate

To a solution of methyl 4-methoxy-3-oxobutanoate (5g, 34.2mmol) in 20ml anhydrous dichloromethane was added triethylamine (5.24ml, 37.6mmol). Reaction was cooled under argon to –78°C to which trifluoromethanesulfonic anhydride (10.6gml, 37.6mmol) was added dropwise via syringe over 5 minutes. Reaction was allowed to warm to room temperature and stirred over night. Next morning the reaction was diluted with 25ml dichloromethane, organic was washed with 2x50ml water, 2x50ml 1N HCl, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude oil was chromatographed on silica gel using a gradient of 5% EtOAc in hexane to 10% EtOAc in hexane as the eluent to give methyl (Z)-4-methoxy-3-{[(trifluoromethyl)sulfonyl]-oxy}-2-butenoate (5.1g, 54%) as a clear colorless oil after drying. H^1NMR ($CDCl_3$) 3.342 (s, 3H); 3.711 (s, 3H); 3.99 (s, H); 6.02 (s, H).

Part B. Methyl (E)-3-(3-cyanophenyl)-4-methoxy-2-butenoate

To a solution of methyl (Z)-4-methoxy-3-{[(trifluoromethyl)sulfonyl]-oxy}-2-butenoate (246mg, 1.0mmol) in 5ml anhydrous dioxane was added potassium phosphate (318mg, 1.5mmol), 3-cyanophenyl boronic acid (162mg, 1.0mmol), and tetrakis (triphenylphosphine)palladium(0) (29mg, 0.0251mmol). Reaction mixture was heated to reflux and stirred overnight. Mixture was filtered through a pad of Celite, diluted with 20ml ethyl acetate. Organic was washed with 2x20ml water, 2x20ml saturated brine solution, dried over magnesium sulfate, filtered and concentrated in vacuo to give methyl (E)-3-(3-cyanophenyl)-4-methoxy-2-butenoate (220mg, 75%) as a clear brown oil which was sufficiently pure to be used without further purification. ES-MS ($M+H^+$): 232.1

Part C. (2E) N-[4-(2-aminosulfonylphenyl)phenyl]-3-methoxymethyl-3-(3-amidinophenyl)-acrylamide.

To a solution of 2'-*t*Butylaminosulfonyl-4-amino-[1,1']-biphenyl (105mg, 0.35mmol) in 4ml anhydrous dichloromethane was added a solution of 2M trimethylaluminum in hexane (0.53ml, 1.05mmol). Reaction was stirred at room temperature for 20 minutes to which a solution of methyl (E) 3-(3-cyanophenyl)-4-methoxy-2-butenoate (80mg, 0.35mmol) in 1ml anhydrous dichloromethane was added. Reaction was stirred at room temperature overnight. Reaction was quenched

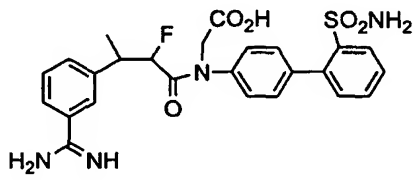
with 5ml 1N HCl after which an additional 20ml dichloromethane was added. Organic was washed with 2x20ml water, dried over magnesium sulfate and concentrated to give (2E)-N-[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]-3-(3-cyanophenyl)-4-methoxybut-2-enamide (150mg, 85%) as a white foam after drying which was sufficiently pure to be used without further purification.

To a solution of (2E)-N-[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]-3-(3-cyanophenyl)-4-methoxybut-2-enamide (150mg, 0.298mmol) in 10ml 1:1 ethyl acetate:anhydrous methanol cooled to –78°C was bubbled HCl gas until saturation was achieved. Reaction was allowed to warm to room temperature and stirred overnight. The reaction was then concentrated in vacuo and dried under hi vacuum. The dried methyl imidate residue was dissolved in 5ml anhydrous methanol to which ammonium acetate (77mg, 1mmol) was added and the reaction heated to reflux for 2 hours. The reaction was concentrated, treated with trifluoroacetic acid (10ml) for 2hrs, concentrated and purified on a 2x25cm Vydac C_{18} HPLC column to give the title compound (34mg, (25%) as a fluffy off-white powder after lyophilization. ES-MS ($M+H^+$): 465.15

Part D. N-[4-(2-aminosulfonylphenyl)phenyl]-3-methoxymethyl-3-(3-amidinophenyl)-propionamide.

To a solution of (2E) N-[4-(2-aminosulfonylphenyl)phenyl]-3-methoxymethyl-3-(3-amidinophenyl)-acrylamide (5mg, 0.01mmol) in 4ml methanol was added 10% Pd on carbon (1mg). Mixture was treated with hydrogen at 1 atmosphere under balloon for 1hr. Reaction was filtered through a pad of Celite, concentrated and lyophilized to give the title compound (5mg, 100%) as a fluffy white powder. ES-MS ($M+H^+$): 467.15

Example 19. Preparation of N-{4-[(2-aminosulfonyl)phenyl]phenyl}-N-(carboxylmethyl)-3-(3-amidinophenyl)-2-fluoro-3-methylpropionamide.



A. Ethyl 3-(3-cyanophenyl)-2-fluoro-3-methylacrylate.

To a solution of triethyl 2-fluoro-2-phosphonoacetate (0.838 mL, 4.13 mmol) in anhydrous THF (25 mL) at –78 C, potassium bis(trimethylsilyl)amide (0.5 M in toluene, 10.0 mL, 5.00 mmol) was added dropwise. After 10 min following the addition, a solution of 3-acetylbenzonitrile (0.600 g, 4.14 mmol) in THF (8 mL) was added dropwise. The reaction mixture was stirred at –78 C for 30 min, then removed to room temperature, and stirred at the temperature overnight. Aqueous NH4Cl and EtOAc were added. Organic phase was separated, washed with sat. NaCl, dried over Na2SO4, concentrated in vacuo to give an oil as a mixture of E- and Z-isomers in a ratio of 5 : 1 (0.920g, yield: 95%), which was pure enough to be used in the next reaction. MS 234 (M + H).

B. N-{4-[(2-tert-butylaminosulfonyl)phenyl]phenyl}-3-(3-cyanophenyl)-2-fluoro-3-methylacrylamide.

To the solution of 4-(2'-tert-butylaminosulfonylphenyl)aniline (0.195 g, 0.641 mmol) in CH2Cl2 (8 mL) at room temperature, trimethylaluminum (2.0 M in hexane, 0.96 mL, 1.92 mmol) was added dropwise. The reaction mixture was stirred for 15 min. A solution of ethyl 3-(3-cyanophenyl)-2-fluoro-3-methylacrylate (0.149 g, 0.639 mmol) in CH2Cl2 (5 mL) was added. It was stirred overnight. 1N HCl was added to neutralize the solution to pH 2-3. Water and CH2Cl2 were added. Organic phase was separated, dried over Na2SO4, concentrated in vacuo to give a solid (0.290 g, yield: 92%), which was pure enough to be used in the next reaction. MS 436 (M + H – ^{t}Bu) and 514 (M + Na).

C. N-{4-[(2-tert-butylaminosulfonyl)phenyl]phenyl}-N-(methoxycarbonylmethyl)-3-(3-cyanophenyl)-2-fluoro-3-methylacrylamide

To a solution of N-{4-[(2-tert-butylaminosulfonyl)phenyl]phenyl}-3-(3-cyanophenyl)-2-fluoro-3-methylacrylamide (230mg, 0.47mmol) in 15ml DMF was added cesium carbonate (460mg, 1.41mmol) and bromomethyl acetate (355mg, 2.35mmol). The reaction mixture was stirred at room temperature for 4 hours then diluted with 25ml of ethyl acetate. Organic was washed with 3x25ml water, 3x25ml saturated brine solution, dried over magnesium sulfate, filtered and concentrated in vacuo to give the title compound (230mg, 86%) as yellow foam. ES-MS ($M+H^+$): 563.2.

D. N-{4-[(2-aminosulfonyl)phenyl]phenyl}-N-(methoxycarbonylmethyl)-3-(3-amidinophenyl)-2-fluoro-3-methylacrylamide

To a solution of N-{4-[(2-tert-butylaminosulfonyl)phenyl]phenyl}-N-(methoxycarbonylmethyl)-3-(3-cyanophenyl)-2-fluoro-3-methylacrylamide (230mg, 0.408mmol) in 10ml 1:1 ethyl acetate:anhydrous methanol cooled to –78°C was bubbled HCl gas until saturation was achieved. Reaction was allowed to warm to room temperature and stirred 18 hours. The reaction was then concentrated in vacuo and dried under hi vacuum. The dried methyl imidate residue was dissolved in 5ml anhydrous methanol to which ammonium acetate (115mg, 1.5mmol) was added and the reaction heated to reflux for 2 hours. The reaction was then concentrated and purified on a 2x25cm Vydac C_{18} HPLC column to give the title compound (150mg, 70%) as a fluffy white powder after lyophilization. ES-MS ($M+H^+$): 525.2.

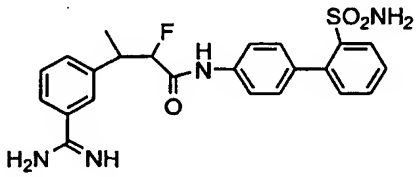
E. N-{4-[(2-aminosulfonyl)phenyl]phenyl}-N-(carboxylmethyl)-3-(3-amidinophenyl)-2-fluoro-3-methylacrylamide

To a solution of N-{4-[(2-aminosulfonyl)phenyl]phenyl}-N-(methoxycarbonylmethyl)-3-(3-amidinophenyl)-2-fluoro-3-methylacrylamide (100mg, 0.19mmol) in 5ml methanol was added a 0.5N lithium hydroxide solution (1ml, 0.5mmol). The reaction was stirred at room temperature for 4 hours then concentrated and purified on a 2x25cm Vydac C_{18} HPLC column to give the title compound (70mg, 71%) as a fluffy white powder after lyophilization. ES-MS ($M+H^+$): 511.1.

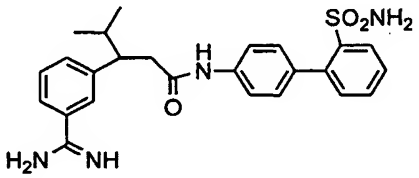
F. N-{4-[(2-aminosulfonyl)phenyl]phenyl}-N-(carboxylmethyl)-3-(3-amidinophenyl)-2-fluoro-3-methylpropionamide.

To a solution of N-{4-[(2-aminosulfonyl)phenyl]phenyl}-N-(carboxylmethyl)-3-(3-amidinophenyl)-2-fluoro-3-methylacrylamide (9mg) in 4ml methanol was added 10% Pd on carbon (2mg). Mixture was treated with hydrogen at 40 psi overnight. Reaction mixture was filtered through a pad of Celite, and concentrated in vacuo. The residue was purified by HPLC to give the title compound (5mg, yield: 56%) as a fluffy white powder. ES-MS ($M+H^+$): 513.1.

Example 20. Preparation of N-{4-[(2-aminosulfonyl)phenyl]phenyl}-3-(3-amidinophenyl)-2-fluoro-3-methylpropionamide. MS ($M+H^+$): 455.1.



Example 21. Preparation of N-{4-[(2-aminosulfonyl)phenyl]phenyl}-3-(3-amidinophenyl)- 3-isopropylpropionamide.



A. Preparation of 3-isopropylbenzenecarbonitrile.

To a mixture prepared by adding copper cyanide (940mg, 10.5mmol) to a cooled solution of lithium bromide (1.82g 21mmol) in tetrahydrofurn at –25°C under argon atmosphere was added a solution of 0.5M 3-cyanophenyl zinc iodide (20ml, 10mmol) in tetrahydrofuran. The reaction mixture was allowed to warm to 0 °C for 30 minutes then cooled down to -25 °C to which neat isobutyryl chloride (1.06ml,

10.1mmol) was added all at once. The reaction was kept at -25 °C for 30 minutes then quenched by adding 20ml of a saturated solution of ammonium chloride. The mixture was extracted with 2x25ml diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo to an oil. The crude oil was flushed through a silica plug using 10% ethyl acetate in hexane to give 3-isopropylbenzenecarbonitrile (1.25g, 72%) as a clear oil. H^1NMR ($CDCl_3$) : 2.2-2.25 (d, 6H); 4.499-4.568 (m, H); 8.614-8.655 (m, 2H); 8.831-8.857 (m, H); 9.172-9.238 (m, H). ES-MS ($M+H^+$): 174.1.

B. Preparation of (2Z) methyl 3-(3-cyanophenyl)-3-isopropylacrylate

To a solution of bis(2,2,2-trifluoromethyl)(methoxy carbonylmethyl)phosphonate (0.38ml, 1.8mmol) in 2.5ml anhydrous tetrahydrofuran was added a solution of 18-Crown-6 (1.9g, 7.5mmol) in 2.5ml anhydrous tetrahydofuran. The reaction mixturewas cooled to -78 °C under argon to which was added a solution of 0.5M bis(trimethylsilyl)amide in toluene (3.6ml, 1.8mmol). The reaction was stirred at -78 °C for 15 minutes to which was added a solution of 3-isopropylbenzenecarbonitrile in 2.5ml anhydrous tetrahydofuran. The reaction was allowed to warm to room temperature and stirred for 48 hours. The reaction was quenched by the addition of 20ml of a saturated ammonium chloride solution followed by extraction with 2x25ml diethyl ether. Combined organic layers were washed with 2x25ml water, 2x25ml saturated brine solution, dried over magnesium sulfate, filtered and concentrated to give a 9:1 mixture of Z and E isomers (420mg, 120%) as a clear oil which was sufficiently pure to use without further purification. ES-MS ($M+H^+$): 230.1.

C. Preparation of (2Z)-N-{4-[(2-tert-butylaminosulfonyl)phenyl]phenyl}-3-(3-cyanophenyl)-3-isopropylacrylamide

To a solution of 2'-tert-butylaminosulfonyl-4-amino-[1,1']-biphenyl (139mg, 0.46mmol) in 4ml anhydrous dichloromethane was added a solution of 2M trimethylaluminum in hexane (0.69ml, 1.38mmol). Reaction was stirred at room temperature for 20 minutes to which a solution of crude methyl (2Z)-3-(3-cyanophenyl)-4-methylpent-2-enoate (105mg, 0.46mmol) in 2ml anhydrous dichloromethane was added. Reaction was stirred at room temperature overnight. Reaction was quenched with 5ml 1N HCl after which an additional 20ml dichloromethane was added. Organic was washed with 2x20ml water, dried over

magnesium sulfate, filtered and concentrated to give the title compound (190mg, 82%) as an off-white foam which was sufficiently pure to be used without further purification. ES-MS ($M+H^+$): 501.2.

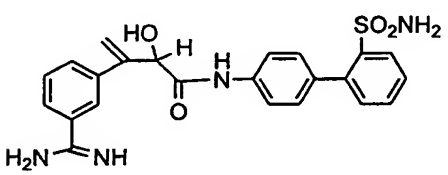
D. Preparation of (2Z)-N-{4-[(2-aminosulfonyl)phenyl]phenyl}-3-(3-amidinophenyl)-3-isopropylacrylamide

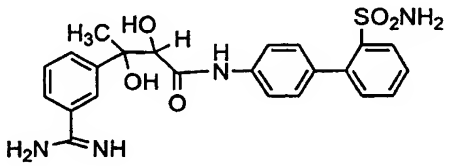
To a solution of crude (2Z)-N-{4-[(2-tert-butylaminosulfonyl)phenyl]phenyl}-3-(3-cyanophenyl)-3-isopropylacrylamide (190mg, 0.379mmol) in 10ml 1:1 ethyl acetate:anhydrous methanol cooled to –78°C was bubbled HCl gas until saturation was achieved. Reaction was allowed to warm to room temperature and stirred overnight. The reaction was then concentrated in vacuo and dried under hi vacuum. The dried methyl imidate residue was dissolved in 5ml anhydrous methanol to which ammonium acetate (115mg, 1.5mmol) was added and the reaction heated to reflux for 2 hours. The reaction was concentrated and purified on a 2x25cm Vydac C_{18} HPLC column to the title compound (75mg, 43%) as a fluffy white powder after lyophilization. ES-MS ($M+H^+$): 463.2.

E. N-[4-(2-aminosulfonylphenyl)phenyl]-3-isopropyl-3-(3-amidinophenyl)-propionamide.

To a solution of (2Z)-N-{4-[(2-aminosulfonyl)phenyl]phenyl}-3-(3-amidinophenyl)-3-isopropylacrylamide (7mg) in 4ml methanol was added 10% Pd on carbon (2mg). Mixture was treated with hydrogen at 1 atmosphere under balloon for 1hr. Reaction was filtered through a pad of Celite, concentrated and lyophilized to give the title compound (7mg, 100%) as a fluffy white powder. ES-MS ($M+H^+$): 465.2.

Example 22. Preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-2-hydroxyl-3-methylidenyl-3-(3-amidinophenyl)-propionamide and N-[4-(2-aminosulfonylphenyl)phenyl]-2,3-dihydroxyl-3-methyl-3-(3-amidinophenyl)-propionamide.





A. tert-Butyl 3-methyl-3-(3-cyanophenyl)-2,3-epoxypropanoate.

To a solution of 3-acetylbenzonitrile (1.45 g, 10 mmol) and tert-butyl chloroacetate (1.43 mL, 10 mmol) in tert-butanol (60 mL) at room temperature, potassium t-butoxide (1.45 g, 12.9 mmol) was added. The reaction mixture was stirred at room temperature overnight. Aqueous ammonium chloride was added to quench the reaction. Ethyl acetate and water were added. The organic phase was separated, washed with brine, dried over Na2SO4, concentrated in vacuo. The residue was purified by a silica gel column, first eluted with hexane, followed by 5% and 10% ethyl acetate in hexane, to give the title compound as a mixture of stereoisomers (1.49 g, yield: 58%). ^{1}H NMR (CDCl3) 7.76 – 7.40 (m, 4H), 3.60 (s, 1H, major isomer, 60%), 3.33 (s, 1H, minor isomer, 40%), 1.80 (s, 3H, minor isomer), 1.75 (s, 3H, major isomer), 1.55 (s, 9H, minor isomer), 1.08 (s, 9H, major isomer).

B. 3-Methyl-3-(3-cyanophenyl)-2,3-epoxypropionic acid.

To a solution of tert-Butyl 3-methyl-3-(3-cyanophenyl)-2,3-epoxypropanoate (0.24 g, 0.93 mmol) in methanol (5 mL), 5 N NaOH (1.0 mL, 5.0 mmol) was added. The solution was stirred at room temperature for 3 hrs. It was neutralized with 6N HCl to pH = 1-2. Ethyl acetate and water were added. The organic phase was separated, washed with brine, dried over Na2SO4, concentrated in vacuo to give an oil (0.17 g, yield: 90%). MS (M+H) 204.

C. N-[4-(2-tert-butylaminosulfonylphenyl)phenyl]-3-methyl-3-(3-cyanophenyl)-2,3-epoxypropionamide.

To solution of 3-Methyl-3-(3-cyanophenyl)-2,3-epoxypropionic acid (168 mg, 0.828 mmol) and 4-(2-tert-butylaminosulfonylphenyl)aniline (252 mg, 0.828 mmol) and triethylamine (0.23 mL, 1.66 mmol) in anhydrous DMF (4 mL), BOP (735 mg, 1.66 mmol) was added. The reaction mixture was stirred at room temperature overnight. Ethyl acetate and water were added. The organic phase was separated, washed with sat. NaHCO3, dried over Na2SO4, concentrated in vacuo to give a solid (402 mg, yield: 99%). MS (M+Na) 512.1; (M+H-tBu) 434.0.

D. N-[4-(2-tert-butylaminosulfonylphenyl)phenyl]-3-methyl-3-(3-amidinophenyl)-2,3-epoxypropionamide.

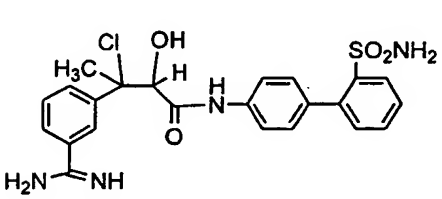
To a solution of N-[4-(2-tert-butylaminosulfonylphenyl)phenyl]-3-methyl-3-(3-cyanophenyl)-2,3-epoxypropionamide (223 mg, 0.456 mmol) in ethanol (6 mL), hydroxylamine hydrochloride (64 mg, 0.92 mmol) was added, followed by addition of triethylamine (0.190 mL, 1.37 mmol). The mixture was heated at 60 C overnight. The solution was concentrated in vacuo. The residue was dissolved in acetic acid (3 mL). To the solution, acetic anhydride (0.217 mL, 2.30 mmol) was added. The reaction mixture was stirred at room temperature for 30 min., then concentrated in vacuo and dried on high vaccuum. The residue was dissolved in methanol (5 mL). To the solution, Palladium on carbon (5%, 25 mg) was added. The mixture was hydrogenated under balloon H2 overnight. The solution was filtered through a plug of celite. The filtrate was concentrated in vacuo. The residue was purified by HPLC to give the title compound (73 mg, yield: 32%). MS (M+H) 507.2.

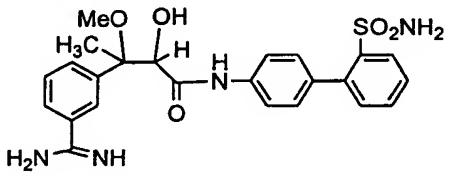
E. N-[4-(2-aminosulfonylphenyl)phenyl]-2-hydroxyl-3-methylidenyl-3-(3-amidinophenyl)-propionamide and N-[4-(2-aminosulfonylphenyl)phenyl]-2,3-dihydroxyl-3-methyl-3-(3-amidinophenyl)-propionamide.

The compound N-[4-(2-tert-butylaminosulfonylphenyl)phenyl]-3-methyl-3-(3-amidinophenyl)-2,3-epoxypropionamide (20 mg, 0.040 mmol) was dissolved in TFA (1 mL). The solution was allowed to stand at room temperature overnight, then concentrated in vacuo. The residue was purified by HPLC to give the product N-[4-(2-aminosulfonylphenyl)phenyl]-2-hydroxyl-3-methylidenyl-3-(3-amidinophenyl)-

propionamide (10 mg) and product N-[4-(2-aminosulfonylphenyl)phenyl]-2,3-dihydroxyl-3-methyl-3-(3-amidinophenyl)-propionamide (5 mg). For compound N-[4-(2-aminosulfonylphenyl)phenyl]-2-hydroxyl-3-methylidenyl-3-(3-amidinophenyl)-propionamide, MS (M+H) 451.1; ^{1}H NMR (CD3OD) 8.09 (d, 1H), 7.91 (d, 1H), 7.90 (s, 1H), 7.68 (d, 1H), 7.63 – 7.47 (m, 5H), 7.36 (d, 2H), 7.30 (d, 1H), 5.67 (d, 2H), 5.18 (s, 1H). For compound N-[4-(2-aminosulfonylphenyl)phenyl]-2,3-dihydroxyl-3-methyl-3-(3-amidinophenyl)-propionamide, MS (M+H) 469.1; ^{1}H NMR (CD3OD) 8.09 (d, 1H), 7.93 (s, 1H), 7.92 (d, 1H), 7.70 – 7.40 (m, 6H), 7.36 (d, 2H), 7.30 (d, 1H), 4.26 (s, 1H), 1.73 (s, 3H).

Example 23. Preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-2-hydroxyl-3-methyl-3-chloro-3-(3-amidinophenyl)-propionamide and N-[4-(2-aminosulfonylphenyl)phenyl]-2-hydroxyl-3-methyl-3-methoxyl-3-(3-amidinophenyl)-propionamide.

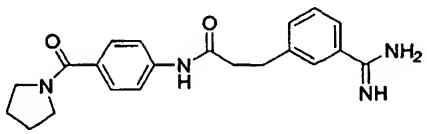




The compound N-[4-(2-tert-butylaminosulfonylphenyl)phenyl]-3-methyl-3-(3-cyanophenyl)-2,3-epoxypropionamide (130 mg, 0.266 mmol), from Part C of Example 22, was dissolved in anhydrous methanol (4 mL). To the solution cooled in ice bath, HCl gas was bubbled through until saturation was reached. It was stirred at room temperature overnight, and then concentrated in vacuo. The residue was dissolve in anhydrous methanol (3mL). To the solution, ammonium acetate (144 mg, 1.87 mmol) was added. The mixture was allowed to stand at room temperature overnight, and then concentrated in vacuo. The residue was purified by HPLC to give the product N-[4-(2-aminosulfonylphenyl)phenyl]-2-hydroxyl-3-methyl-3-chloro-3-(3-amidinophenyl)-propionamide (35 mg) and product N-[4-(2-aminosulfonylphenyl)phenyl]-2-hydroxyl-3-methyl-3-methoxyl-3-(3-amidinophenyl)-propionamide (11 mg). For compound N-[4-(2-aminosulfonylphenyl)phenyl]-2-hydroxyl-3-methyl-3-chloro-3-(3-amidinophenyl)-propionamide, MS (M+H) 487.0 and 489.0 (chlorine pattern); ^{1}H NMR (CD3OD)

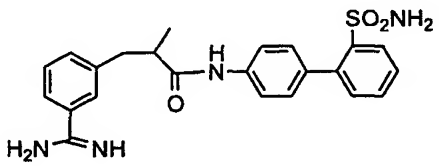
8.07(d, 1H), 8.05 (d, 1H), 8.00 (s, 1H), 7.75 – 7.28 (m, 9H), 4.68 (s, 1H, major isomer, 65%), 4.60 (s, 1H, minor isomer, 35%), 2.21 (s, 3H, minor isomer), 2.18 (s, 3H, major isomer). For compound N-[4-(2-aminosulfonylphenyl)phenyl]-2-hydroxyl-3-methyl-3-methoxyl-3-(3-amidinophenyl)-propionamide, MS (M+H) 483.1; ^{1}H NMR (CD3OD) 8.09(d, 1H), 7.88 (d, 1H), 7.80 (s, 1H), 7.77 – 7.29 (m, 9H), 4.30 (s, 1H, minor isomer, 40%), 4.27 (s, 1H, major isomer, 60%), 3.25 (s, 3H, minor isomer), 3.23 (s, 3H, major isomer), 1.82 (s, 3H, minor isomer), 1.78 (s, 3H, major isomer).

Example 24. Preparation of N-[4-(1-pyrrolidinylcarbonyl)phenyl]-3-(3-amidinophenyl)-propionamide.



The compound was prepared analogously to preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-(3-amidinophenyl)-propionamide in Example 1. MS (M+H) 365.1.

Example 25. Preparation of N-{4-[(2-aminosulfonyl)phenyl]phenyl}-3-(3-amidinophenyl)-2-methylpropionamide



Part A. Ethyl (Z)-3-(3-cyanophenyl)-2-methyl-2-butenoate

A solution of 1.00 g (3.0 mmol) of ethyl 2-[bis(2,2,2-trifluoroethyl)phosphono]-propionate (*Synth. Comm.*, **1991**, *21*, 2391) and 3.9 g (5 eq) of 18-crown-6 in 25 mL of anhydrous THF was cooled with a dry ice-acetone bath, and 7.0 mL of a 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene were added. The solution was stirred in the cold for 20 min, then a solution of 400 mg (3.05 mmol) of 3-cyanobenzaldehyde in 10 of anhydrous THF was added dropwise over a few minutes. The reaction was stirred in the cold for 1 hr, then allowed to warm to room temperature over 3 hr, quenched by the addition of 10 mL of saturated aqueous ammonium chloride, and extracted with 2 x 50 mL of ether. The organic layer was washed with 50 mL of water, followed by 50 mL of saturated NaCl, then dried over $MgSO_4$. Filtration and concentration gave 1 g of a light yellow oil, which was washed through a plug of silica gel with 200 mL of CH_2Cl_2. Concentration then gave 586 mg (97%) of the desired product as a light yellow oil, which was >90% the desired (Z)-isomer by ^1H NMR: ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H), 3.64 (s, 3H), 6.68 (s, 1H), 7.1-7.3 (m, 1H), 7.35-7.55 (m, 3H).

Part B. (2Z)-N-[4-(2{[(N-1,1-dimethylethyl)amino]sulfonyl}phenyl)phenyl]-3-(3-cyanophenyl)-2-methylacrylamide

To a solution of 103 mg (0.34 mmol) of 4'-amino-N-(1,1-dimethylethyl)-[1,1'-biphenyl]-2-sulfonamide in 5 mL of anhydrous CH_2Cl_2 was added 0.5 mL of a 2.0 M solution of trimethylaluminum in hexanes, and the solution was stirred at room temperature for 30 minutes. A solution of 103 mg of ethyl (Z)-3-(3-cyanophenyl)-2-methyl-2-butenoate in 5 mL of anhydrous CH_2Cl_2 was then added dropwise over a few minutes, and the reaction was stirred at room temperature overnight. The reaction was then carefully quenched by the addition of 10 mL of 1N HCl, and the reaction mixture was then partitioned between 100 mL of CH_2Cl_2 and 50 mL of H_2O. The organic layer was dried over $MgSO_4$, filtered and concentrated to give a solid residue, which was subjected to flash column chromatography on silica gel using 10% EtOAc in hexanes to give 104 mg (65%) of the desired product as a white solid: ^1H NMR ($CDCl_3$) δ 1.00 (s, 9H), 2.22 (s, 3H), 3.60 (s, 1H), 6.59 (s, 1H), 7.15-7.6 (m, 12H), 8.14 (d, J = 7.6 Hz, 1 H).

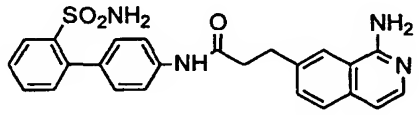
Part C. (2Z)-N-{4-[(2-aminosulfonyl)phenyl]phenyl}-3-(3-amidinophenyl)-2-methylacrylamide

A suspension of 50 mg of the above nitrile in 10 mL of anhydrous methanol was cooled with an ice-water bath, and HCl gas was bubbled into the solution at a moderate rate for 10 min. The reaction was then closed with a rubber septum and stirred at room temperature overnight. The reaction was concentrated to give a semisolid residue, which was taken up in 5 mL of anhydrous methanol, and 41 mg of vacuum dried ammonium acetate were added. The solution was heated at gentle reflux for 1.5 hr, then concentrated to give a white solid. Preparative HPLC (gradient elution with water:acetonitrile each containing 0.1% TFA on C18) then afforded 44 mg of the desired product as a white solid: ^{1}H NMR (DMSO-d_6) δ 2.17 (s, 3H), 6.59 (s, 1H), 7.25-7.35 (m, 5H), 7.5-7.65 (m, 6H), 7.71 (d, J = 5.6 Hz, 1H), 8.01 (d, J = 7.6 Hz, 1H), 8.95 (s, 2H), 9.31 (s, 2H). 10.25 (s, 1H). MS 435.1.

Part D. N-{4-[(2-aminosulfonyl)phenyl]phenyl}-3-(3-amidinophenyl)-2-methylpropanamide

A solution of 14 mg of the alkene from Part C and 5 drops of triethyamine in 5 mL of methanol, together with 10 mg of 10% Pd/C was placed under a balloon of hydrogen and stirred overnight. The reaction was filtered and concentrated, and the residue was subjected to preparative HPLC (gradient elution with water:acetonitrile each containing 0.1% TFA on C18) to give 7 mg of the desired product as a white solid: ^{1}H NMR (CD_3OD) δ 1.24 (d, J = 6.4 Hz, 3H), 2.82 (d, J = 9.2 Hz, 2H), 3.02 (m, 1H), 7.2-7.65 (m, 11H), 8.02 (d, J = 7.6 Hz, 1H). MS (M+H) 437.1.

Example 26. N-{4-[(2-aminosulfonyl)phenyl]phenyl}-3-(1-aminoisoquinolin-7-yl)-propionamide



Part A. 7-Bromoisoquinoline

This compound was prepared as a 60:40 mixture with 5-bromoisoquinoline as in *J. Am. Chem. Soc.*, **1939**, *61*, 183.

Part B. 7-Bromoisoquinoline N-oxide hydrochloride

This compound was prepared by a procedure analogous to that for 6-bromoisoquinoline N-oxide hydrochloride as in PCT WO 98/47876. A solution of 7.8 g (37.5 mmol) of a 60:40 mixture of 7-bromo and 5-bromoisoquinoline in 125 mL of CH_2Cl_2 was treated portionwise with 9.7 g (~39.4 mmol) of 3-chloroperoxybenzoic acid (~70% purity). The solution, which was initially homogeneous, deposited a voluminous precipitate over 1 hr. Then 100 mL of methanol were added, and the reaction was concentrated to a volume of about 100 mL. Gaseous HCl was then bubbled through the solution for about 10 min, during which time the solution became warm and all of the precipitate dissolved. A few minutes later, another voluminous precipitate began to form. To this solution was added 100 mL of ether, and the mixture was stirred in an ice-water bath for 20 minutes. The resulting product was isolated by filtration, washed thoroughly with ether, and air-dried to give 8.07 g (83%) of the desired compound as a white solid, which was still a 60:40 mixture of the 7- and 5-bromo isomers.

Part C. 7-Bromo-1-chloroisoquinoline

This compound was prepared by a procedure analogous to that for 6-bromo-1-chloroisoquinoline as in PCT WO 98/47876. A solution of 8.07 g (31 mmol) of the mixture from Part B was taken up in 50 mL of $POCl_3$, and the mixture was heated at 90 °C for 2 hr. The reaction mixture was concentrated to remove most of the $POCl_3$, and the residue was taken up in 100 mL of CH_2Cl_2. The solution was carefully basified to pH 10 by the slow addition of 1N NaOH, and the organic layer was washed with 100 mL of H_2O, 100 mL of sat. NaCl, and dried over $MgSO_4$. Filtration and concentration gave a light yellow solid, which was subjected to flash column chromatography on silica gel first with 5% and then with 10% EtOAc in hexanes. A total of 3.62 g (48%) of the desired 7-bromo-1-chloroisoquinoline was isolated from this chromatography free of the 5-bromo isomer.

Part D. 7-Bromo-1-phenoxyisoquinoline

A solution of 3.60 g (14.8 mmol) of 7-bromo-1-chloroisoquinoline and 1.5 g of solid KOH in 11.2 g of phenol was heated at 140 °C for 2 hr. The reaction was

cooled to room temperature, then partitioned between 100 mL of CH_2Cl_2 and 100 mL of 3N NaOH. The organic layer was washed with another 2 x 100 mL of 3N NaOH, then with 100 mL of H_2O, and dried over $MgSO_4$. Filtration and concentration gave a yellow oil, which was subjected to flash column chromatography on silica gel 30% CH_2Cl_2 in hexanes, giving 3.42 g (77%) of the desired product as a light yellow solid.

Part E. 1-Amino-7-bromoisoquinoline

A mixture of 3.40 g (11.3 mmol) of 1-amino-7-bromoisoquinoline and 7.65 g of ammonium acetate was heated at 150 °C for 15 hr. The reaction was cooled, and the residue was partitioned between 200 mL of EtOAc and 200 mL of 3N NaOH. The organic layer was extracted with 2 x 100 mL of 2N HCl, and the combined aqueous extracts were basified to pH 10 using 50% NaOH. This solution was extracted with 2 x 100 mL of EtOAc, and the organics were then washed with 100 mL of sat. NaCl and dried over MgSO4. Filtration and concentration gave 1.68 g (66%) of the desired amino compound as a yellow solid.

Part F. 1-[Bis(t-butoxycarbonyl)amino]-7-bromoisoquinoline

A solution of 740 mg (3.32 mmol) of 1-amino-7-bromoisoquinoline in 50 mL of acetonitrile was treated with 1.4 mL of N,N-diiospropylethylamine and 100 mg of 4-(N,N-dimethylamino)pyridine, followed by 3.0 g (4.1 eq) of di-t-butyldicarbonate, and the reaction was stirred at 40 °C for 1 hr. By HPLC analysis, there was still some starting amino compound that remained , so another 1.0 g of di-t-butyldicarbonate were added, and the reaction was stirred at 40 °C for another 30 min. The reaction mixture was concentrated to give a dark oil, which was subjected to flash column chromatography on silica gel with 20% EtOAc in hexanes to give 736 mg of the desired product as a light yellow solid. Also isolated were 156 mg of product as a somewhat less pure light yellow solid, making the total yield 64%.

Part G. 1-[Bis(t-butoxycarbonyl)amino]isoquinoline-7-carboxaldehyde

A solution of 400 mg (0.95 mmol) of 1-[bis(t-butoxycarbonyl)amino]-7-bromoisoquinoline in 50 mL of anhydrous THF was cooled with a liquid nitrogen/methanol slush bath (-98 °C), and 0.55 mL of a 2.43 M solution of n-BuLi

in hexanes (1.3 eq) was added dropwise over 1 min. The solution was stirred in the cold for 5 min, then a solution of 5 mL of anhydrous DMF in 10 mL of anhydrous THF was added rapidly. The solution was allowed to warm to about 0 °C, then poured into 50 mL of 0.5 N HCl, and 50 mL of EtOAc were added. The aqueous layer was brought to pH 6 with 1N NaOH, 25 mL of sat. NaCl were added, and the layers were shaken and separated. The organic layer was dried over Mg SO_4, filtered, and concentrated to give an oily residue. This residue was subjected to flash column chromatography on silica gel with 20% EtOAc in hexanes to give 190 mg (54%) of the desired aldehyde as a yellow semisolid.

Part H. (2Z)-3-{[1-bis(t-butoxycarbonyl)amino]isoquinolin-7-yl}acrylic acid, 2-(trimethylsilyl)ethyl ester

A solution of 117 mg (0.29 mmol) of [bis(2,2,2-trifluoroethoxy)phosphinyl]acetic acid, 2-(trimethylsilyl)ethyl ester (*J. Org. Chem.*, **1991**, *56*, 4204) and 400 mg of 18-crown-6 in 25 mL of anhydrous THF was cooled with a dry ice-acetone bath under Ar, and 0.75 mL of a 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene were added dropwise over 2 min. The reaction was stirred in the cold for 15 min, then a solution of 100 mg (0.27 mmol) of 1-[bis(t-butoxycarbonyl)amino]isoquinoline-7-carboxaldehyde in 25 mL of anhydrous THF was added dropwise over 10 min. The reaction was then allowed to warm to room temperature overnight, then partitioned between 100 mL of CH_2Cl_2 and 50 mL of H_2O. The organics were washed with aqueous NaCl, and dried over $MgSO_4$. Filtration and concentration gave an oily residue, which was subjected to flash column chromatography on silica gel with 25% EtOAc in hexanes to give 33 mg of the desired product as a clear, colorless oil.

Part I. (2Z)-N-[4-(2{[(N-1,1-dimethylethyl)amino]sulfonyl}phenyl)phenyl]-3-{[1-bis(t-butoxycarbonyl)amino]isoquinolin-7-yl}acrylamide

A solution of 63 mg (0.12 mmol) of (2Z)-3-{[1-bis(t-butoxycarbonyl)amino]isoquinolin-7-yl}acrylic acid, 2-(trimethylsilyl)ethyl ester in 1 mL of DMF was treated at room temperature with 150 μL of 1.0 M tetrabutylammonium fluoride in THF overnight. The reaction mixture was directly subjected to preparative HPLC (gradient elution with water:acetonitrile each containing 0.1% TFA on C18) to give, after lyophilization, 21 mg of the desired acid

as a white solid. A solution of this acid and 18 mg of 4'-amino-N-(1,1-dimethylethyl)-[1,1'-biphenyl]-2-sulfonamide in 2 mL of anhydrous DMF, together with 40 μL of N,N-diisopropylethylamine, was treated at room temperature with 25 mg (1.3 eq) of HATU, and the reaction was stirred at room temperature for 1 hr. The reaction mixture was dissolved in 100 mL of CH_2Cl_2, washed with 2 x 25 mL of sat. $NaHCO_3$, and dried over $MgSO_4$. Filtration and concentration gave 53 mg of the desired product as a yellow oily residue, which was used in the next reaction without further purification.

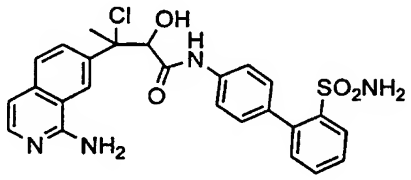
Part J. (2Z)-N-{4-[(2-aminosulfonyl)phenyl]phenyl}-3-(1-aminoisoquinolin-7-yl)-acrylamide

A solution of the yellow oil from Part I in 2 mL of TFA was stirred first in an ice-water bath, and then at room temperature overnight. The reaction mixture was concentrated and directly subjected to preparative HPLC (gradient elution with water:acetonitrile each containing 0.1% TFA on C18) to give 10 mg of the desired product as an off-white solid.

Part K. N-{4-[(2-aminosulfonyl)phenyl]phenyl}-3-(1-aminoisoquinolin-7-yl)-propionamide

A solution of 11 mg of (2Z)-N-{4-[(2-aminosulfonyl)phenyl]phenyl}-3-(1-aminoisoquinolin-7-yl)-acrylamide in 10 mL of methanol, together with a few mg of 10% Pd/C was placed under a balloon of hydrogen gas for 1 hr. At this time, the reaction was complete by HPLC (the retention time was the same as the starting material, but the UV spectrum had changed significantly). The reaction mixture was filtered and concentrated to give the crude product as an oil. A small amount of water was added, and the mixture was lyophilized to give the desired compound as a white solid: ^{1}H NMR (CD_3OD) δ 2.80 (t, J = 7.2 Hz, 2H), 3.23 (t, J = 7.6 Hz, 2H), 7.16 (d, J = 6.8 Hz, 1H), 7.27 (d, J = 7.2 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.45-7.5 (m, 4H), 7.56, (app t, J = 7.2 Hz, 1 H), 7.84 (d, J = 8.4 Hz, 1 H), 7.90 (app d, J = 8.0 Hz, 1H), 8.05 (app d, J = 8.0 Hz, 1H). 8.26 (s, 1H). . MS (M+H) 447.1.

Example 27. Preparation of 3-(1-amino(7-isoquinolyl))-3-chloro-2-hydroxy-N-[4-(2-sulfamoylphenyl)phenyl]butanamide



A. Preparation of 7-isoquinolyl (trifluoromethyl)sulfonate

To a solution of 7-hydroxyisoquiniline (5.50g, 37.9mmol) in 100ml CH_2Cl_2 was added triethylamine (8.00ml, 57.4mmol) dropwise. Then DMAP (0.275g, 2.24mmol) was added. The reaction was stirred for 5min before being cooled to 0°C for 15min. Tf_2O (9.5ml, 56.5mmol) was added and the reaction was allowed to warm to room temperature overnight. Water and DCM were added and separated. The aqueous layer was extracted two more times with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel, first eluded with 20/80 EtOAc/hexanes, then 25/85 EtOAc/hexanes and finally with 30/70 EtOAc/hexanes to give the title compound (5.12g). MS 278 (M + H)

B. Preparation of isoquinoline-7-carbonitrile

To a solution of $Pd_2(dba)_3$ (0.958g, 0.926mmol) and dppf (1.80g, 3.25mmol) in DMF (18ml) was added 7-isoquinolyl (trifluoromethyl)sulfonate (5.12g, 18.5mmol). Heat reaction mixture to 70°C and add $Zn(CN)_2$ (1.30g, 11.10mmol) in three portions (~0.43g each) every 15min. The reaction was allowed to stir for 3 hours before being quenched with water and extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel, first eluded with 20/80 EtOAc/hexanes, 25/85 EtOAc/hexanes, 30/70 EtOAc/hexanes, and 35/75 EtOAc/hexanes to give the title compound (1.75g). MS 155 (M + H)

C. Preparation of 1-(7-isoquinolyl)ethan-1-one

To a solution of isoquinoline-7-carbonitrile (0.496g, 3.22mmol) in 20ml Et_2O at 0°C was added MeMgBr (13.8ml, 19.3mmol) dropwise. The reaction was allowed to stir at room temperature for ~3hrs before being quenched with saturated NH_4Cl. The mixture was neutralized to pH=8 with 5M NaOH, then extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel, first eluded with 20/80 EtOAc/hexanes, 25/85 EtOAc/hexanes, 30/70 EtOAc/hexanes, and 35/75 EtOAc/hexanes to give the title compound (0.389g). MS 172 (M + H)

D. Preparation of tert-butyl 3-(7-isoquinolyl)-3-methyloxirane-2-carboxylate

To a solution of 1-(7-isoquinolyl)ethan-1-one (0.109g, 0.637mmol) in tBuOH (7ml) was added t-butyl chloroacetate (0.182mL, 1.27mmol) then K^{t}BuO (0.147g, 1.31mmol). The reaction was heated to 40°C for 2 hr. Reaction not complete therefore more t-butyl chloroacetate (0.091ul, 0.53mmol) was added. The reaction was heated for a few more hours before being quenched with AcOH (1ml). Water and EtOAc were added. Aqueous layer was extracted twice more with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to a residue (0.206g). MS 286 (M+H)

E. Preparation of 3-(7-isoquinolyl)-3-methyloxirane-2-carboxylic acid

To a solution of tert-butyl 3-(7-isoquinolyl)-3-methyloxirane-2-carboxylate in MeOH (5ml) was added 5M NaOH (0.75ml, 3.75mmol). The reaction was allowed to stir for 2hrs before being concentrated and purified by Preparatory HPLC to yield the title compound (0.402g). MS 230 (M+H)

F. Preparation of N-[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl](3-(7-isoquinolyl)-3-methyloxiran-2-yl)carboxamide

To a solution of N-[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl](3-(7-isoquinolyl)-3-methyloxiran-2-yl)carboxamide (0.40g, 1.76mmol), {[2-(4-aminophenyl)phenyl]sulfonyl}(tert-butyl)amine (0.53g, 1.75mmol), and BOP in DMF(10ml) was added TEA (0.981ml, 7.04mmol) dropwise. The reaction was

stirred at room temperature for 3hrs. Water and EtOAc were added. The aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel to yield the title compound (0.237g, 0.46mmol). MS 516 (M+H)

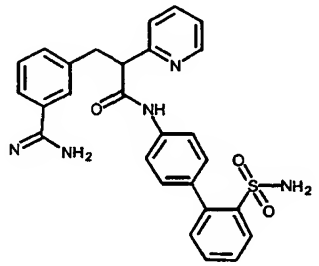
G. Preparation of [3-(1-amino(7-isoquinolyl))-3-methyloxiran-2-yl]-N-[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]carboxamide

To a solution of N-[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl](3-(7-isoquinolyl)-3-methyloxiran-2-yl)carboxamide in acetone (8ml) was added MCPBA (0.091g, max 77%, 0.29mmol). Approximately 1hr later more MCPBA (0.034g, 1.06mmol) was added. Approximately 1hr later the reaction mixture was concentrated and the residue was dissolved in sat. $NaHCO_3$ and EtOAc. The aqueous layer was extracted once more with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in pyridine (7ml) and tosyl chloride (0.066g, 0.346mmol). The reaction was allowed to stir overnight before being concentrated. The residue was dissolved in ~5ml ethanolamine and allowed to stir for a few hours. Water was added to the reaction and the solid was collected MS 531 (M+H)

H. Preparation of 3-(1-amino(7-isoquinolyl))-3-chloro-2-hydroxy-N-[4-(2 sulfamoylphenyl)phenyl]butanamide

To a solution of [3-(1-amino(7-isoquinolyl))-3-methyloxiran-2-yl]-N-[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]carboxamide (0.060g, 1.13mmol) in MeOH (5ml) was bubbled HCl gas to saturation. The reaction was capped with a septum and allowed to stir overnight. Preparatory HPLC purification using10/90 acetonitrile (containing 0.1% TFA) /HQ water (containing 0.1%TFA) to 70/30 acetonitrile (containing 0.1% TFA) /HQ water (containing 0.1% TFA) over 60minutes gave the title compound. MS 511 (M+H)

Example 28. Preparation of 3-(2-(2-pyridyl)-2-{N-[4-(2-sulfamoylphenyl)phenyl]carbamoyl} ethyl)benzenecarboxamidine



A. Preparation of ethyl (2Z)-3-(3-cyanophenyl)-2-(2-pyridyl)prop-2-enoate

A solution of 3-cyanobenzaldehyde (0.797g, 6.07mmol), ethyl 2-pyridylacetate (0.670ml, 6.07mmol) and ammonium acetate (0.566g, 7.39mmol) in acetic acid (3ml) was refluxed overnight. The reaction was cooled to room temperature and neutralized to pH=7 with 5M $NaOH/H_2O$. EtOAc was added and the aqueous layer was washed twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel, first eluded with 10/90 EtOAc/hexanes, 20/80 EtOAc/hexanes, 30/70 EtOAc/hexanes, 35/65 EtOAc/hexanes, 40/60 EtOAc/hexanes, 45/55 EtOAc/hexanes and finally with 50/50 EtOAc/hexanes to give the title compound (0.407g). MS 279 (M + H)

B. Preparation of (2Z)-N-[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]-3-(3-cyanophenyl)-2-(2-pyridyl)prop-2-enamide

To a mixture of ethyl (2Z)-3-(3-cyanophenyl)-2-(2-pyridyl)prop-2-enoate (0.210g, 0.758mmol) and {[2-(4-aminophenyl)phenyl]sulfonyl}(tert-butyl)amine (0.235g, 0.773mmol) in CH_2Cl_2 (5ml) was added $AlMe_3$ (2ml of 2M in hexane, 4mmol). The mixture was allowed to stir overnight before quenching with 6M HCl. The aqueous layer was extracted twice more with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel, first elude with 20/80 EtOAc/hexanes, 30/70 EtOAc/hexanes, 40/60 EtOAc/hexanes, 45/55 EtOAc/hexanes, 50/50 EtOAc/hexanes, 55/45

EtOAc/hexanes, 60/40 EtOAc/hexanes, 70/30 EtOAc/hexanes, then with 80/20 EtOAc/hexanes to give the title compound (0.040g). MS 536 (M + H)

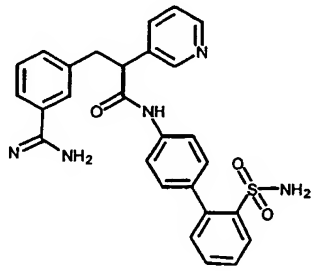
C. Preparation of 3-((1Z)-2-(2-pyridyl)-2-{N-[4-(2-sulfamoylphenyl)phenyl]carbamoyl}vinyl)benzenecarboxamidine

Through a mixture of (2Z)-N-[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]-3-(3-cyanophenyl)-2-(2-pyridyl)prop-2-enamide (0.226g, 0.421mmol) in MeOH (7ml) was bubbled HCl gas to saturation. The reaction was capped with a septum and allowed to run overnight. The reaction was concentrated and the residue was dissolved in MeOH (7ml) to which was added NH_4OAc (0.194g, 2.56mmol). The mixture was refluxed for 4hrs before being concentrated. The residue was purified by preparatory HPLC 10/90 acetonitrile (containing 0.1% TFA) /HQ water (containing 0.1% TFA) to 90/10 acetonitrile (containing 0.1% TFA) /HQ water (containing 0.1% TFA) over 80minutes to yield the title compound (0.212g). MS 498 (M+H)

D. Preparation of 3-(2-(2-pyridyl)-2-{N-[4-(2-sulfamoylphenyl)phenyl]carbamoyl}ethyl)benzenecarboxamidine

A mixture of 3-((1Z)-2-(2-pyridyl)-2-{N-[4-(2-sulfamoylphenyl)phenyl]carbamoyl}vinyl) (0.043g, 0.087mmol) Pd/C (5mg) in MeOH (4ml) with a H_2 balloon was allowed to stir overnight. The reaction was filtered over celite and concentrated. Preparatory purification yielded the target compound. MS 500 (M+H)

Example 29. Preparation of 3-(2-(3-pyridyl)-2-{N-[4-(2-sulfamoylphenyl)phenyl]carbamoyl} ethyl)benzenecarboxamidine



A. Preparation of ethyl (2Z)-3-(3-cyanophenyl)-2-(3-pyridyl)prop-2-enoate

A solution of 3-cyanobenzaldehyde (0.795g, 6.05mmol), ethyl 3-pyridylacetate (0.666ml, 6.07mmol) and ammonium acetate (0.569g, 7.387mmol) in acetic acid (3ml) was refluxed overnight. The reaction was cooled to room temperature and neutralized to pH=7 with 5M $NaOH/H_2O$. EtOAc was added and the aqueous layer was washed twice with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel, first eluded with 10/90 EtOAc/hexanes, 20/80 EtOAc/hexanes, 30/70 EtOAc/hexanes, 35/65 EtOAc/hexanes, 40/60 EtOAc/hexanes, 45/55 EtOAc/hexanes and finally with 50/50 EtOAc/hexanes to give the title compound (0.365g). MS 279 (M + H)

B. Preparation of (2Z)-N-[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]-3-(3-cyanophenyl)-2-(3-pyridyl)prop-2-enamide

To a mixture of ethyl (2Z)-3-(3-cyanophenyl)-2-(3-pyridyl)prop-2-enoate (0.208g, 0.749mmol) and {[2-(4-aminophenyl)phenyl]sulfonyl}(tert-butyl)amine (0.228g, 0.750mmol) in CH_2Cl_2 (5ml) was added $AlMe_3$ (1.2ml of 2M in hexane, 2.4mmol). The mixture was allowed to stir overnight before quenching with 6M HCl. The aqueous layer was extracted twice with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel, first elude with 30/70 EtOAc/hexanes, 40/60 EtOAc/hexanes, 50/50 EtOAc/hexanes, 60/40 EtOAc/hexanes to give the title compound (0.157g). MS 536 (M + H)

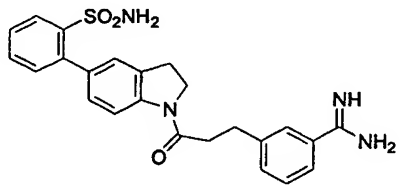
C. Preparation of 3-((1Z)-2-(3-pyridyl)-2-{N-[4-(2-sulfamoylphenyl)phenyl]carbamoyl}vinyl)benzenecarboxamidine

Through a mixture of (2Z)-N-[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]-3-(3-cyanophenyl)-2-(3-pyridyl)prop-2-enamide (0.157g, 0.293mmol) in MeOH (7ml) was bubbled HCl gas to saturation. The reaction was capped with a septum and allowed to run overnight. The reaction was concentrated and the residue was dissolved in MeOH (7ml) to which was added NH_4OAc (0.138g, 1.79mmol). The mixture was refluxed for 4hrs before being concentrated. The residue was purified by preparatory HPLC 5/95 acetonitrile (containing 0.1% TFA) /HQ water (containing 0.1% TFA) to 95/5 acetonitrile (containing 0.1% TFA) /HQ water (containing 0.1% TFA)water over 90minutes to yield the title compound (0.237g). MS 498 (M+H)

D. Preparation of 3-(2-(3-pyridyl)-2-{N-[4-(2-sulfamoylphenyl)phenyl]carbamoyl}ethyl)benzenecarboxamidine

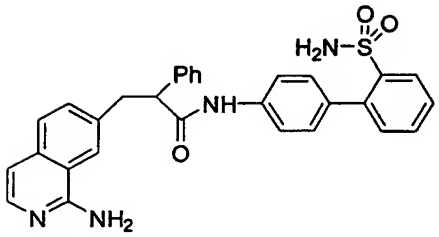
A mixture of 3-((1Z)-2-(3-pyridyl)-2-{N-[4-(2-sulfamoylphenyl)phenyl]carbamoyl}vinyl)benzenecarboxamidine (0.053g, 0.087mmol) Pd/C (5mg) in MeOH (5ml) with a H_2 balloon was allowed to stir overnight. The reaction was filtered over celite and concentrated. The residue was purified by preparatory HPLC 5/95 acetonitrile (containing 0.1% TFA) /HQ water (containing 0.1% TFA) water to 95/5 acetonitrile (containing 0.1% TFA) /HQ water (containing 0.1% TFA) water over 60minutes to yield the title compound (0.016g). MS 500 (M+H)

Example 30. Preparation of [5-(2-aminosulfonylphenyl)indolin-1-yl] 3-(3-amidinophenyl)-propionyl amide.



The compound was prepared analogously to preparation of N-[4-(2-aminosulfonylphenyl)phenyl]-3-(3-amidinophenyl)-propionamide in Example 1. MS (M+H) 449.1.

Example 31. Preparation of 3-(1-aminoisoquinol-7yl)-2-phenyl-N-[4-(2-sulfamoylphenyl)phenyl]propionamide



A. Preparation of ethyl 2-phenylprop-2-enoate

A mixture of ethyl 2-phenylacetate (15.9 mL, 100 mmol), paraformaldehyde (4.5 g, 150 mmol), K2CO3 (22.11 g, 100 mmol) and Bu4NI (0.7388 g, 2 mmol) in toluene was heated to 80-90 C for 40 h. Standard workup (saturated NaCl solution washing) yielded 14.78 g (84%) of the titled compound. MS 177 (M+1).

B. Preparation of ethyl 3-(7-isoquinolyl)-2-phenylprop-2-enoate

trans-Di(μ-acetato)bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (0.1654 g, 0.18 mmol) was added to a solution of 7-isoquinolyl (trifluoromethyl)sulfonate (1.70 g, 7 mmol), ethyl 2-phenylprop-2-enoate (2.26 g, 7mmol), and triethyl amine (1.95 mL, 14 mmol) in DMF (50 mL). After stirring for 16 h at 120 C, Pd catalyst (0.1654 g, 0.18 mmol) was added again, and the suspension was stirred for 16 h at 120 C. After standard workup (filtration and washing with saturated NaCl solution), the crude brown oil was purified by Prep HPLC to yield the titled compound 1.06 g (50%). MS 304 (M + 1).

C. Preparation of N-[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]-3-(7-isoquinolyl)-2-phenylpropanamide

To a solution of compound ethyl 3-(7-isoquinolyl)-2-phenylprop-2-enoate (172.5 mg, 0.57 mmol) in anhydrous MeOH (10 mL) was added 10% Pd/C (600 mg). The solution was then stirred under hydrogen ballon (1 atm) for 6 h. The hydrogenated product of ethyl 3-(7-isoquinolyl)-2-phenylpropanoate was collected by the removal of the solvent in *vacuo*, and carried over to the next step directly.

To a solution of 4-(2-tert-butylaminosulfonylphenyl)aniline (171.9 mg, 0.57 mmol) in CH2Cl2 (10 mL) at room temperature, trimethylaluminum (0.848 mL, 2.0 M in hexane, 1.7 mmol) was added dropwise. After the solution was stirred for 30 min at room temperature, compound ethyl 3-(7-isoquinolyl)-2-phenylpropanoate from the last reaction was added. The mixture was stirred at room temperature for 1 days. The solution was neutralized with 1N HCl (10 mL) to pH = 1-2. Water and CH2Cl2 were added, and organic phase was separated, dried over Na2SO4, concentrated in *vacuo* to give a yellowish soild, which was further purified by Prep HPLC to yield the titled compound 198.9 mg (yield: 62%). MS 564 (M+1).

D. Preparation of 3-(1-amino(7-isoquinolyl))-2-phenyl-N-[4-(2-sulfamoylphenyl)phenyl]propanamide

To a solution of N-[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]-3-(7-isoquinolyl)-2-phenylpropanamide (31 mg, 0.06 mmol) in acetone (5 mL) at 23 C was added mCPBA (20 mg, 0.08 mmol). The mixture was stirred at this temperature for 18 h. The solvent was removed in *vacuo*. The residue was partitioned between EtOAc and saturated NaHCO3 solution. The organic layers were collected, dried over Na2SO4 and concentrated in *vacuo*.

The crude product was dissolved in dry pyridine (5 mL) and TsCl (15.7 mg, 0.08 mmol) was added. The mixture was stirred at 23 C for 5 minutes. The solvent of pyridine was removed in *vacuo*. The residue was dissolved in ethanolamine (5 mL). The mixture was stirred at 23 C for 3 h before pouring into saturated NaCl solution for partition. The organic layers were collected and concentrated in *vacuo* to afford a yellow residue.

The residue was dissolved in TFA (5 mL). The mixture was stirred at 23 C for 18 h. The solvent was removed in *vacuo* and the crude product was further purified by Prep HPLC to yield the titled compound 10 mg (32%). MS 523 (M+1).

BIOLOGICAL ACTIVITY EXAMPLES

Evaluation of the compounds of this invention is guided by in vitro protease activity assays (see below) and in vivo studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters.

The compounds of the present invention are dissolved in buffer to give solutions containing concentrations such that assay concentrations range from 0 to 100 μM. In the assays for thrombin, prothrombinase and factor Xa, a synthetic chromogenic substrate is added to a solution containing test compound and the enzyme of interest and the residual catalytic activity of that enzyme is determined spectrophotometrically. The IC_{50} of a compound is determined from the substrate turnover. The IC_{50} is the concentration of test compound giving 50% inhibition of the substrate turnover. The compounds of the present invention desirably have an IC_{50} of less than 500 nM in the factor Xa assay, preferably less than 200 nM, and more preferred compounds have an IC_{50} of about 100 nM or less in the factor Xa assay. The compounds of the present invention desirably have an IC_{50} of less than 4.0 μM in the prothrombinase assay, preferably less than 200 nM, and more preferred compounds have an IC_{50} of about 10 nM or less in the prothrombinase assay. The compounds of the present invention desirably have an IC_{50} of greater than 1.0 μM in the thrombin assay, preferably greater than 10.0 μM, and more preferred compounds have an IC_{50} of greater than 100.0 μM in the thrombin assay.

Amidolytic Assays for determining protease inhibition activity

The factor Xa and thrombin assays are performed at room temperature, in 0.02 M Tris·HCl buffer, pH 7.5, containing 0.15 M NaCl. The rates of hydrolysis of the para-nitroanilide substrate S-2765 (Chromogenix) for factor Xa, and the substrate Chromozym TH (Boehringer Mannheim) for thrombin following

preincubation of the enzyme with inhibitor for 5 minutes at room temperature, and were determined using the Softmax 96-well plate reader (Molecular Devices), monitored at 405 nm to measure the time dependent appearance of p-nitroaniline.

The prothrombinase inhibition assay is performed in a plasma free system with modifications to the method described by Sinha, U. *et al.*, Thromb. Res., 75, 427-436 (1994). Specifically, the activity of the prothrombinase complex is determined by measuring the time course of thrombin generation using the p-nitroanilide substrate Chromozym TH. The assay consists of preincubation (5 minutes) of selected compounds to be tested as inhibitors with the complex formed from factor Xa (0.5 nM), factor Va (2 nM), phosphatidyl serine:phosphatidyl choline (25:75, 20 μM) in 20 mM Tris·HCl buffer, pH 7.5, containing 0.15 M NaCl, 5 mM $CaCl_2$ and 0.1% bovine serum albumin. Aliquots from the complex-inhibitor mixture are added to prothrombin (1 nM) and Chromozym TH (0.1 mM). The rate of substrate cleavage is monitored at 405 nm for two minutes. Eight different concentrations of inhibitor are assayed in duplicate. A standard curve of thrombin generation by an equivalent amount of untreated complex are used for determination of percent inhibition.

Antithrombotic Efficacy in a Rabbit Model of Venous Thrombosis

A rabbit deep vein thrombosis model as described by Hollenbach, S. et al., Thromb. Haemost. 71, 357-362 (1994), is used to determine the in-vivo antithrombotic activity of the test compounds. Rabbits are anesthetized with I.M. injections of Ketamine, Xylazine, and Acepromazine cocktail. A standardized protocol consists of insertion of a thrombogenic cotton thread and copper wire apparatus into the abdominal vena cava of the anesthetized rabbit. A non-occlusive thrombus is allowed to develop in the central venous circulation and inhibition of thrombus growth is used as a measure of the antithrombotic activity of the studied compounds. Test agents or control saline are

administered through a marginal ear vein catheter. A femoral vein catheter is used for blood sampling prior to and during steady state infusion of test compound. Initiation of thrombus formation begins immediately after advancement of the cotton thread apparatus into the central venous circulation. Test compounds are administered from time = 30 min to time = 150 min at which the experiment is terminated. The rabbits are euthanized and the thrombus excised by surgical dissection and characterized by weight and histology. Blood samples are analyzed for changes in hematological and coagulation parameters.

Effects of Compounds in Rabbit Venous Thrombosis model

Administration of compounds in the rabbit venous thrombosis model demonstrates antithrombotic efficacy at the higher doses evaluated. There are no significant effects of the compound on the aPTT and PT prolongation with the highest dose (100 μg/kg + 2.57 μg/kg/min). Compounds have no significant effects on hematological parameters as compared to saline controls. All measurements are an average of all samples after steady state administration of vehicle or (D)-Arg-Gly-Arg-thiazole. Values are expressed as mean ± SD.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods.

WHAT IS CLAIMED IS:

1. A compound according to the formula:

A-Y-D-E-G-J-Z-L

wherein:

A is selected from:

(a) phenyl, which is independently substituted with 0-2 R^1 substituents;

(b) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^1 substituents;

(c) naphthyl, which is independently substituted with 0-2 R^1 substituents;

(d) C_1-C_6-alkyl; C_3-C_8-cycloalkyl; and

(e) $-NR^2R^3$, $-C(=NR^2)NR^2R^3$, $-NR^2C(=NR^2)NR^2R^3$, $-C(=NR^2)R^4$, and $NR^2C(=NR^2)-R^3$

R^1 is selected from:

Halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl,-CN, $-NO_2$, $-(CH_2)_mNR^2R^3$, $-C(=O)NR^2R^3$, $-C(=NR^2)NR^2R^3$, $-NR^2C(=NR^2)NR^2R^3$, $-C(=NR^2)R^4$ and $NR^2C(=NR^2)-R^3$, $-SO_2NR^2R^3$, $-SO_2R^2$, $-CF_3$, $-OR^2$, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl and $-NO_2$;

R^2 and R^3 are independently selected from the group consisting of:

H, $-OR^{14}$, $-NR^{14}R^{15}$, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, $COOC_{1-4}$alkyl, COO-C_{0-4}alkylphenyl C_{0-4}alkylphenyl

and C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and $-NO_2$;

m is an integer of 0-2;

Y is a member selected from the group consisting of:

a direct link, -C(=O)-, $-N(R^4)$-, $-C(=O)-N(R^4)$-, $-N(R^4)-C(=O)$-, $-SO_2$-, -O-, $-SO_2-N(R^4)$-, $-N(R^4)-SO_2$-, $-C(=NR^4)$, -C(=S)-, $-CH_2$-, $-CH_2N(R^4)$-;

R^4 is selected from:

H, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, C_{0-4}alkylphenyl and C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and $-NO_2$;.

D is a direct link or is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0-2 R^{1a} substituents;

(b) naphthyl, which is independently substituted with 0-2 R^{1a} substituents; and

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1a} substituents;

R^{1a} is selected from:

Halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, $-NO_2$, $(CH_2)_mNR^{2a}R^{3a}$, $SO_2NR^{2a}R^{3a}$, SO_2R^{2a}, CF_3, OR^{2a}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on

the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN and $-NO_2$;

m is an integer of 0-2;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, C_{0-4}alkylphenyl and C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN and $-NO_2$;.

E is a member selected from the group consisting of:

$-N(R^5)-C(=O)-$, $-C(=O)-N(R^5)-$, $-N(R^5)-C(=O)-N(R^6)-$, $-SO_2-N(R^5)-$, $-N(R^5)-SO_2-N(R^6)-$ and $-N(R^5)-SO_2-N(R^6)-C(=O)-$;

R^5 and R^6 are independently selected from:

H, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, C_{0-4}alkylphenyl, C_{0-4}alkylnaphthyl, C_{0-4}alkylheteroaryl, C_{1-4}alkylCOOH and C_{1-4}alkylCOOC_{1-4}alkyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl, naphthyl and heteroaryl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN and $-NO_2$;

G is selected from:

$-CR^7R^8-$ and $-CR^{7a}R^{8a}-C^bR^{8b}$

Wherein R^7, R^8, R^{7a}, R^{8a}, R^{7b} and R^{8b} are each independently a member selected from the group consisting of:

hydrogen, halo, $-C_{1-6}$alkyl, haloalkyl, -CN, $-NO_2$, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkyl-C_{3-8}-cycloalkyl, $-C_{0-4}$alkyl-CN, $-C_{0-}$

$_4$alkyl-NO_2, -C_{0-4}alkyl-O-R^9, -C_{0-4}alkyl-S-R^9, -C_{0-4}alkyl-S(=O)$_2$-R^9, -C_{0-4}alkyl-S(O)-R^9, -C_{0-4}alkyl-C(=O)-OR^9, -C_{0-4}alkyl-C(=O)-N(R^{9a}, R^{9b}), -C_{0-4}alkyl-C(=O)-R^9, -C_{0-4}alkyl-N(R^{9a}, R^{9b}), -C_{0-4}alkyl-N(-R^{9a})-C(=O)-R^{9b}), -C_{0-4}alkyl-N(-R^{9a})-C(=O)-R^{9b}, -C_{0-4}alkyl-N(-R^{9a})-C(=O)-N(-R^{9b}), -C_{0-4}alkyl-N(-R^{9a})-S(=O)$_2$-R^{9b}, -C_{0-4}alkyl-S(=O)$_2$-N(R^{9a}, R^{9b}), -C_{0-4}alkyl-S(=O)$_2$-R^9, -C_{0-4}alkyl-P(=O)(-OR^{9a})(-OR^{9b}), -C_{0-4}alkyl-N(-R^9)-P(=O)(-OR^{9a})(-OR^{9b}), -C_{0-4}alkyl-phenyl, -C_{0-4}alkyl-naphthyl, -C_{0-4}alkyl-heterocyclic ring system containing from 1-4 heteroatoms selected from the group consisting of O, N and S, wherein the heterocyclic ring system is a 5-6 membered monocyclic ring or a 8-12 membered bicyclic ring, and wherein 0-4 hydrogen atoms of the phenyl ring, the naphthyl ring carbon and the heterocyclic ring system are replaced by a member selected from the group consisting of -C_{1-4}alkyl, haloalkyl, halo, -CN, -NO_2, -OR^{9c}, -SR^{9c}, -S(O)R^{9c}, -C(=O)-OR^{9c}, -C(=O)-N(-R^{9c}, R^{9d}), -C(=O)-R^{9c}, -N(R^{9c}, R^{9d}), -N(-R^{9c})-C(=O)-R^{9d}, -N(-R^{9c})-C(=O)-OR^{9d}, -N(-R^{9c})-C(=O)-N(-H, R^{9d}), -N(-R^{9c})-SO_2-R^{9d}, -SO_2-N(-R^{9c}, -R^{9d}), -SO_2-R^{9c}; or one of R^7, R^8, R^{7a}, R^{8a}, R^{7b} and R^{8b} can combine with a nitrogen on the E group to form a 5-7 membered heterocyclic ring containing a 0-3 additional heteroatoms selected from the group consisting of O, N and S; or R^{7a} and R^{7b} on adjacent carbons combine to form a 3-6 membered carbocyclic ring;

R^{7b} and R^{8b} combine to form alkylidene groups, such as H_2C=, C_{1-4}alkylCH=, (C_{1-4}alkyl)$_2$C=, PhCH=;

R^9, R^{9a}, R^{9b}, R^{9c} and R^{9d} are each independently a member selected from the group consisting of:

H, halo -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkyl-C_{3-8}cycloalkyl, -CH_2CH_2OH, -CH_2CH_2-O-CH_3, -C_{0-4}alkylphenyl, -C_{0-4}alkylheterocycle wherein the heterocycle may be a 5-6 membered ring, and wherein from 0-4 hydrogen atoms from the ring atoms of the phenyl and heterocycle groups may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkyl-C_{3-8}cycloalkyl, -CN, -NO_2, -C(=O)-OH, -C(=O)-O-C_{1-4}alkyl, -C(=O)-NH_2, -C(=O)-N(-H, -C1-4alkyl), and -C(=O)-N(-C_{1-4}alkyl, -C_{1-4}alkyl);

alternatively, R^{9a} taken with R^{9b} or R^{9c} taken with R^{9d} when either pair of groups is attached to the same nitrogen atom may combine with that nitrogen atom to form a 5-8 membered saturated, partially saturated or unsaturated ring which contains from 0-1 additional heteroatoms selected from a group consisting of -N, -O, S, wherein any S ring atom may be present as a -S-, -S(=O)- or -$S(=O)_2$- group;

J is a member selected from the group consisting of:

a direct link, -$CH(R^{11})$- and -$CH(R^{11})$-CH_2-;

R^{11} is a member selected from the group consisting of:

hydrogen, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkyl-C_{3-8}cycloalkyl, C_{0-4}alkylphenyl, C_{0-4}alkylnaphthyl, C_{0-4}alkylheterocyclic ring having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S, CH_2COOC_{1-4}alkyl, CH_2COOC_{1-4}alkylphenyl and CH_2COOC_{1-4}alkylnaphthyl;

Z is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0-2 R^{1b} substituents;

(b) naphthyl, which is independently substituted with 0-2 R^{1b} substituents; and

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R^{1b} substituents;

R^{1b} is selected from:

Halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, -NO_2, $NR^{2b}R^{3b}$, $SO_2NR^{2b}R^{3b}$, SO_2R^{2b}, CF_3, OR^{2b}, O-CH_2-CH_2-OR^{2b}, O-CH_2-$COOR^{2b}$, N(R^{2b})-CH_2-CH_2-OR^{2b}, N(-CH_2-CH_2-OR^{2b})$_2$, N(R^{2b})-C(=O)R^{3b}, N(R^{2b})-SO_2-R^{3b}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be

independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN and $-NO_2$;

R^{2b} and R^{3b} are independently selected from the group consisting of:

H, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, C_{0-4}alkylphenyl and C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN and $-NO_2$;

L is selected from:

H, -CN, $C(=O)NR^{12}R^{13}$, $(CH_2)_nNR^{12}R^{13}$, $C(=NR^{12})NR^{12}R^{13}$, $NR^{12}R^{13}$, OR^{12}, $-NR^{12}C(=NR^{12})NR^{12}R^{13}$, and $NR^{12}C(=NR^{12})-R^{13}$;

n is an integer of 0-2;

R^{12} and R^{13} are independently selected from:

hydrogen, $-OR^{14}$, $-NR^{14}R^{15}$, C_{1-4}alkyl, C_{0-4}alkylphenyl, C_{0-4}alkylnaphthyl, $COOC_{1-4}$alkyl, COO-C_{0-4}alkylphenyl and COO-C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and $-NO_2$;

R^{14} and R^{15} are independently selected from:

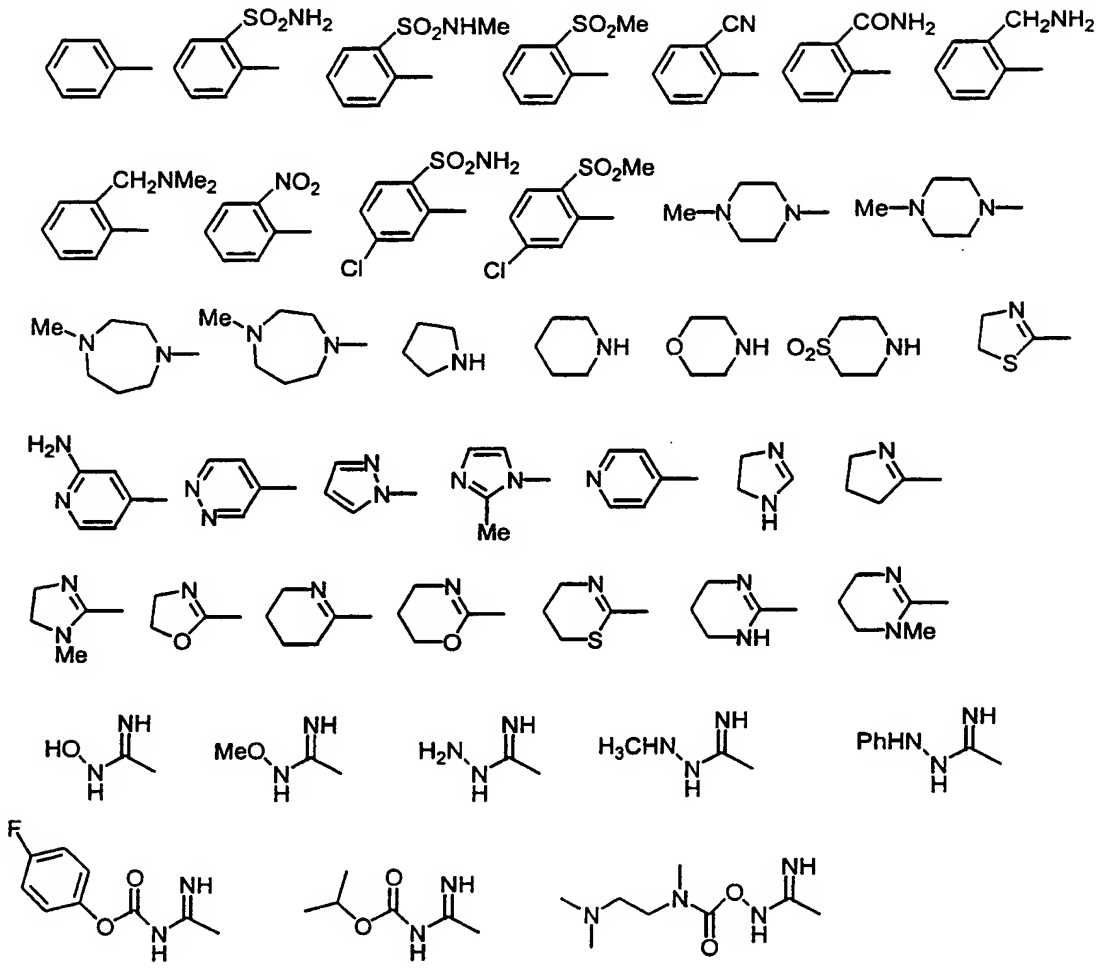
H, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, C_{0-4}alkylphenyl and C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and $-NO_2$;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and

prodrug derivatives thereof.

2. A compound according to claim 1, wherein:

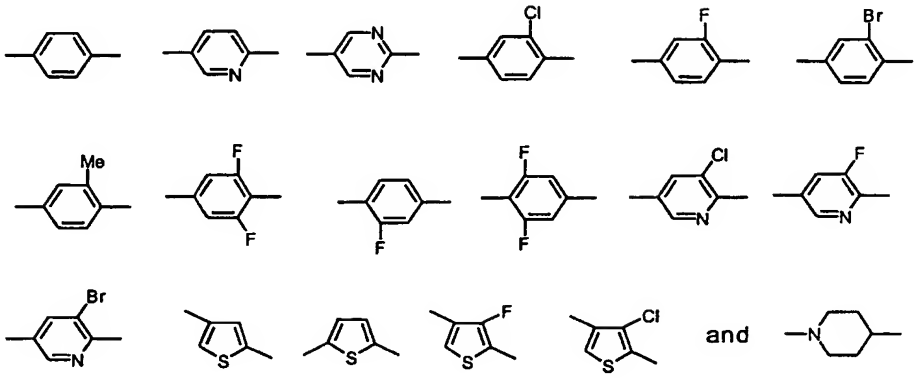
A is a member selected from the group consisting of:



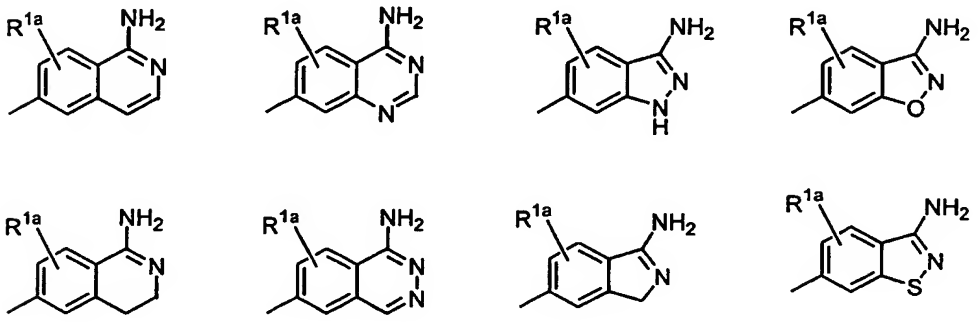
Y is a member selected from the group consisting of:

a direct link, -C(=O)-; -N(-CH_3)-; -N(CH_3)-CH_2-; -C(=NH)-, -CH_2-, –C(=S)-, -NH-, and -SO_2-;

D is a member selected from the group consisting of:



or A-Y-D is a member selected from the group consisting of:



Wherein R^{1a} is selected from:

hydrogen, Cl, F, Br, Me, OMe, NO_2, CO_2H, CN, $C(=O)NH_2$, and C(=O)OMe;

E is a member selected from the group consisting of:

-N(-H)-C(=O)-and -C(=O)-N(-H)-;

G is $-CR^{7a}R^{8a}-C^{b}R^{8b}$;

wherein R^{7a}, R^{8a}, R^{7b} and R^{8b} are independently a member selected from the group consisting of:

hydrogen, F, Cl, Br, -OH, $-NO_2$, -CN, $-C_{1-4}$alkyl, haloalkyl, $-OR^9$, $-CH_2OR^9$, $-S(=O)_2-R^9$, $-CH_2S(=O)_2-R^9$, $-C(=O)-OR^9$, $-CH_2C(=O)-OR^9$, $-C(=O)-N(R^{9a}, R^{9b})$, $-CH_2C(=O)-N(R^{9a}, R^{9b})$, $-N(R^{9a}, R^{9b})$, $-CH_2N(R^{9a}, R^{9b})$, $-N(R^{9a})-C(=O)-R^{9b}$), phenyl, benzyl, $-C_{0-2}$alkyl-heterocyclic ring system containing from 1-4 heteroatoms selected from the group consisting of O, N and S, wherein the heterocyclic ring system is a 5-6 membered monocyclic ring; wherein the phenyl ring and heterocyclic ring are substituted by a member selected from the group consisting of CH_3, halo, -CN, $-NO_2$, -OMe, $-CO_2H$, $-CO_2Me$;

or R^{7b} and R^{8b} combine to form $CH_2=$, $(CH_3)_2C=$, PhCH=;

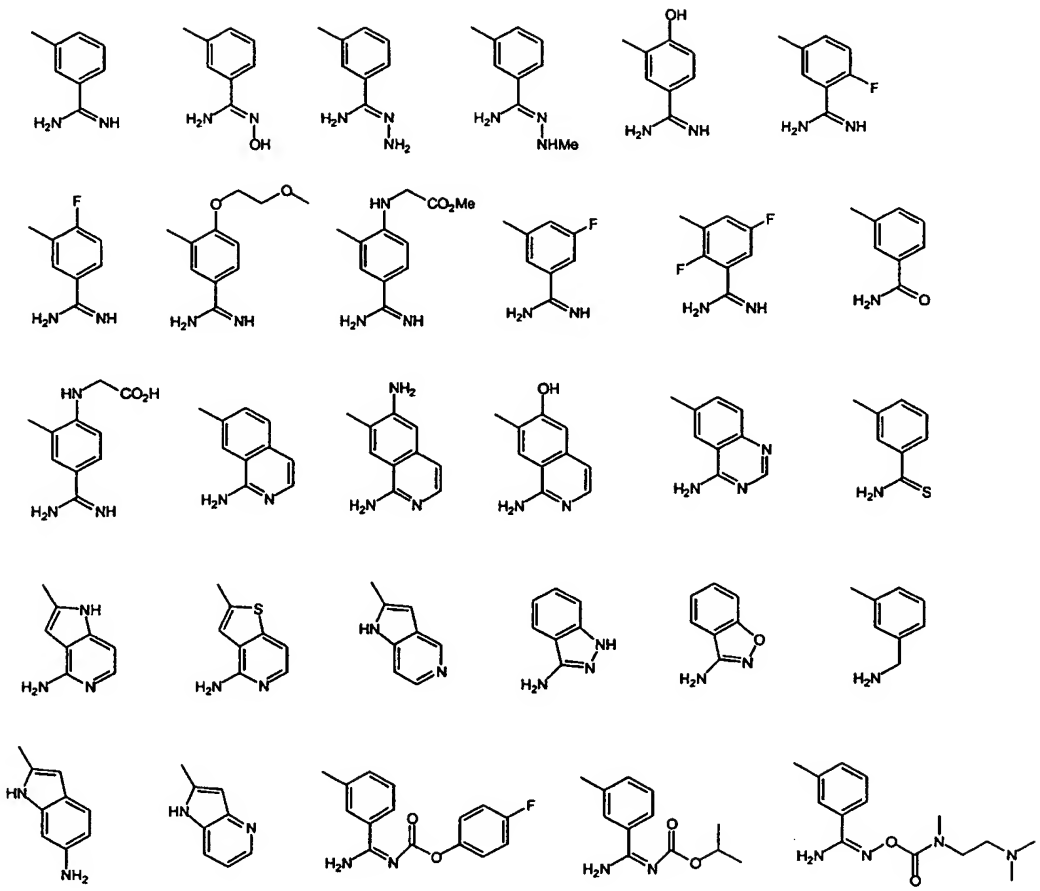
R^9, R^{9a} and R^{9b} are independently selected from:

hydrogen, $-C_{1-4}$alkyl, haloalkyl, phenyl, benzyl; or R^{9a} and R^{9b} may combine with that nitrogen atom to which they are attached to form a 5-6 membered ring which contains from 0-1 additional heteroatoms selected from a group consisting of -N, -O, S;

J is a member selected from the group consisting of:

a direct link, $-CH_2-$;

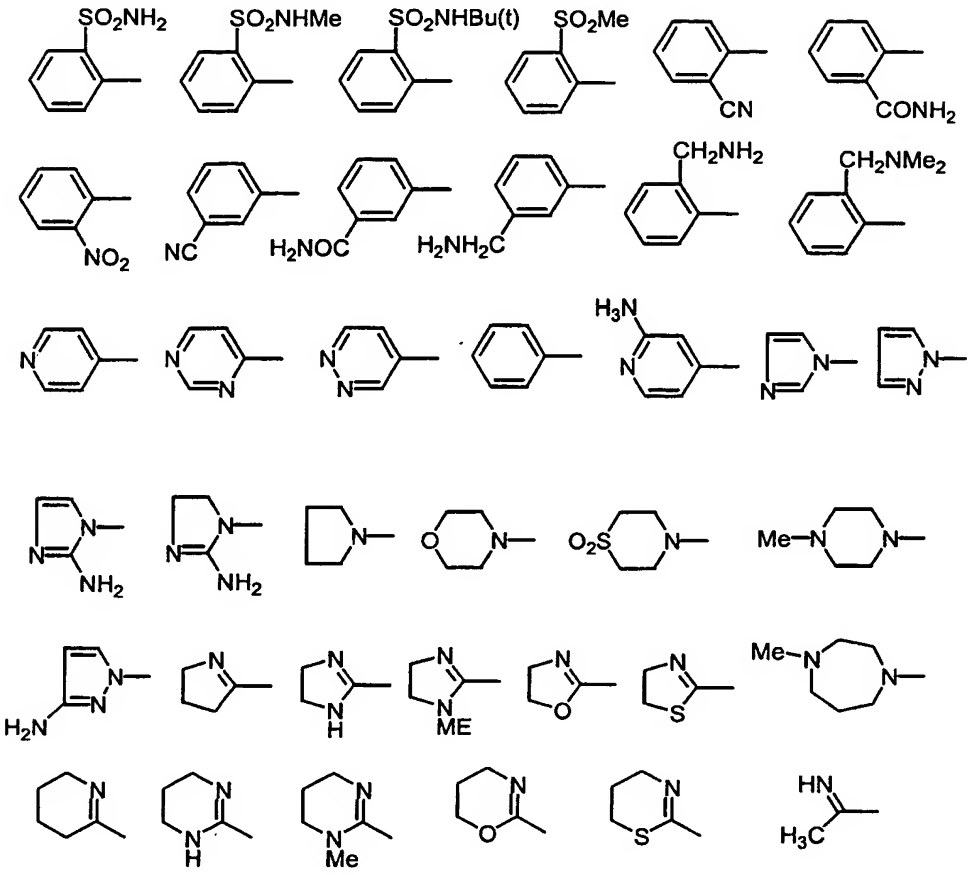
Z-L is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

3. A compound according to claim 1, wherein:

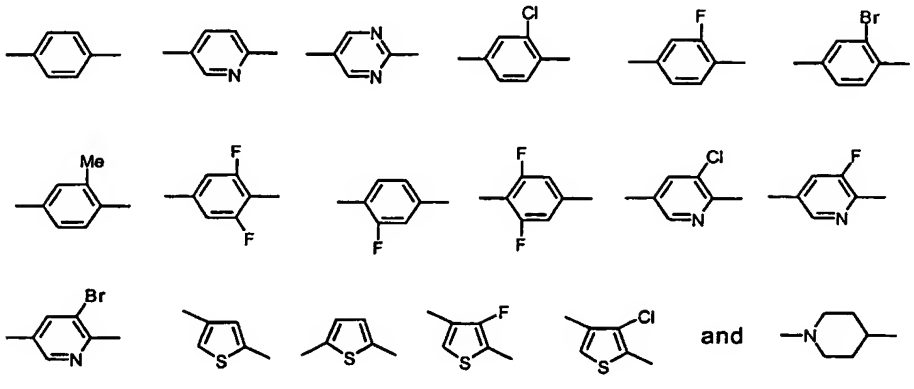
A is a member selected from the group consisting of:



Y is a member selected from the group consisting of:

a direct link, -C(=O)-; -N(-CH_3)-; -N(CH_3)-CH_2-; -C(=NH)-, -CH_2-, –C(=S)-, -NH-, and -SO_2-;

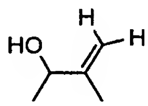
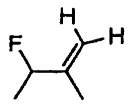
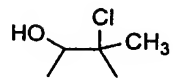
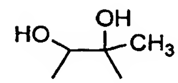
D is a member selected from the group consisting of:

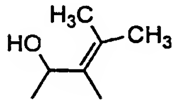
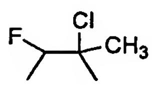
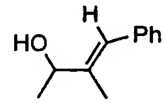
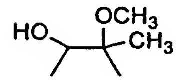


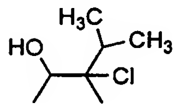
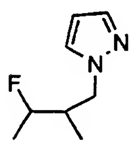
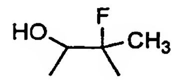
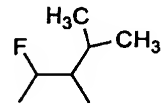
E is a member selected from the group consisting of:

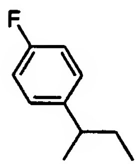
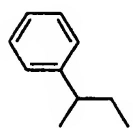
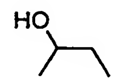
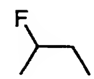
-N(-H)-C(=O)-and -C(=O)-N(-H)-;

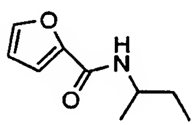
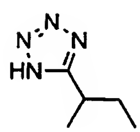
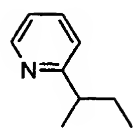
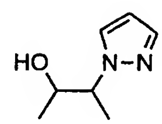
G is a member selected from the group consisting of:

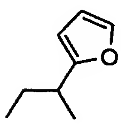
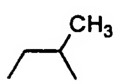
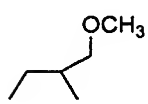
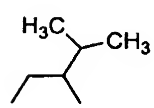
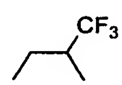
   

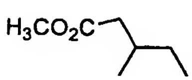
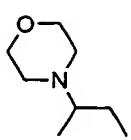
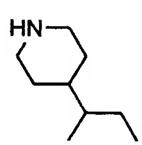
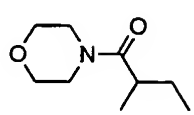
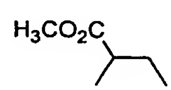
   

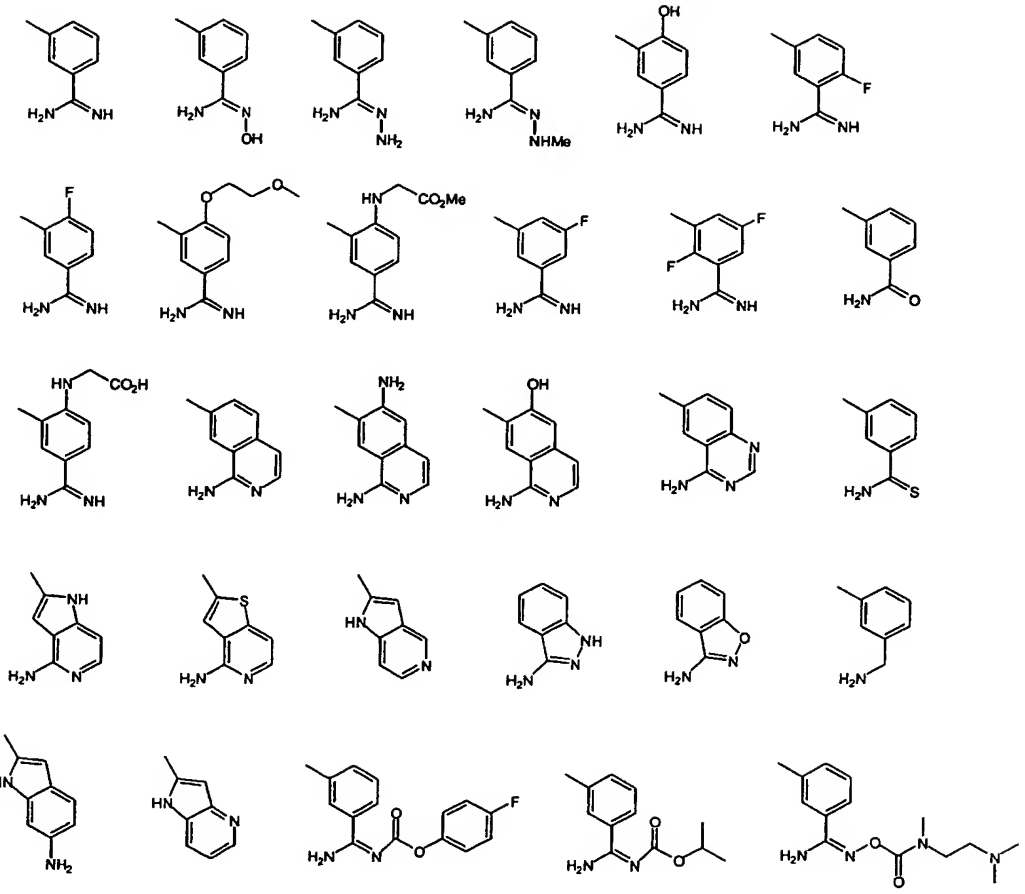
    

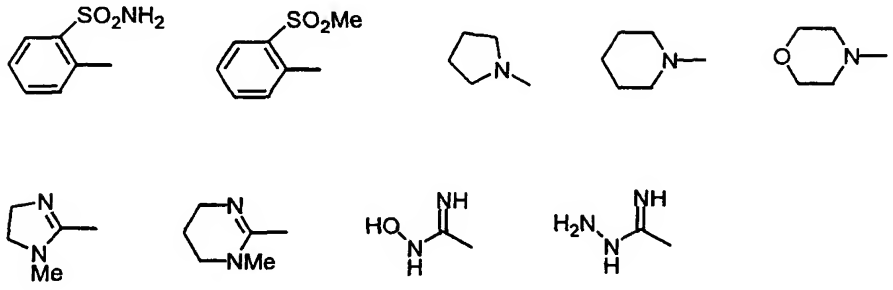
J is a direct link;

Z-L is a member selected from the group consisting of:



4. A compound according to claim 1, wherein

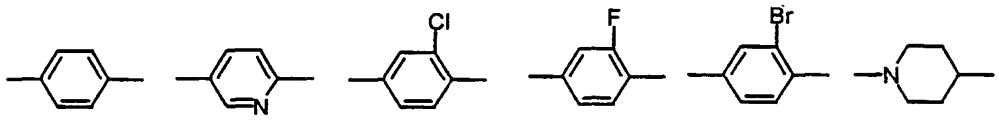
A is a member selected from the group consisting of:



Y is a member selected from the group consisting of:

a direct link, -C(=O)-; -N(-CH_3)-; -N(CH_3)-CH_2-; -C(=NH)-, -CH_2-, –C(=S)-, -NH-, and -SO_2-;

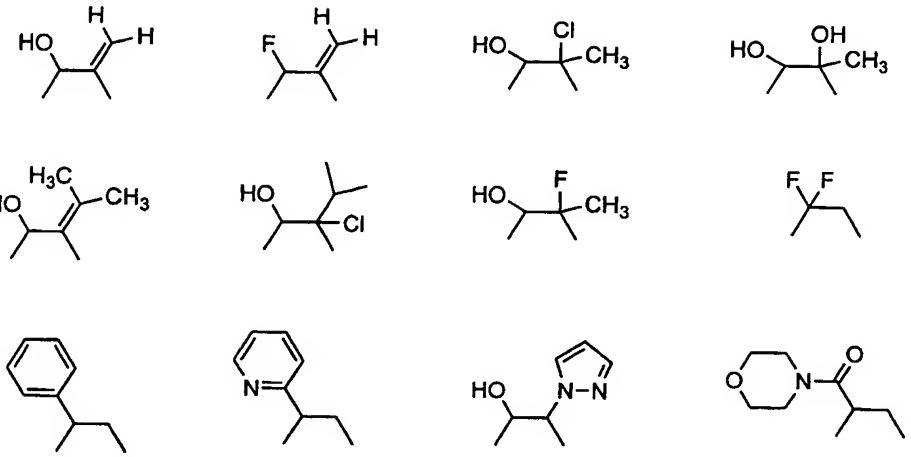
D is a member selected from the group consisting of:



E is a member selected from the group consisting of:

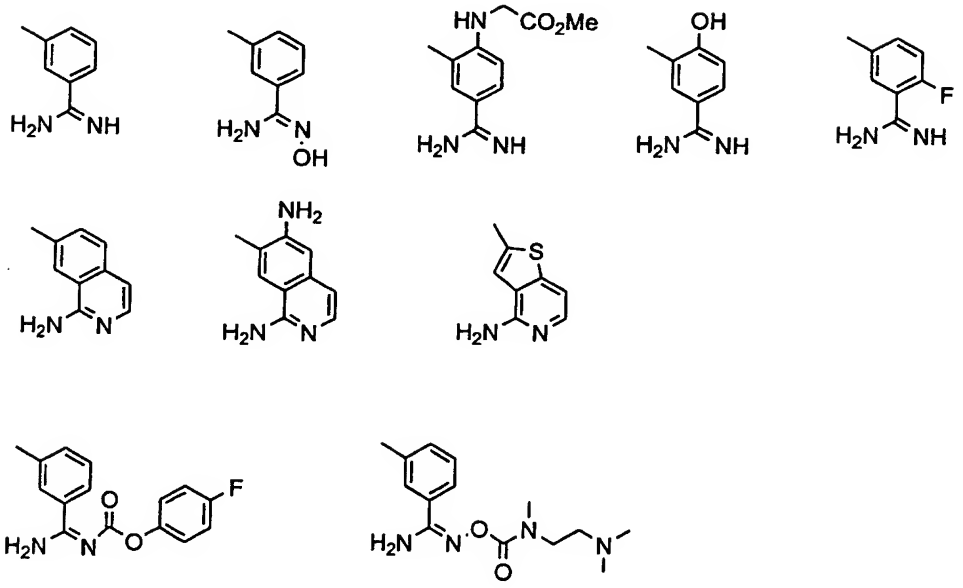
-N(-H)-C(=O)-and -C(=O)-N(-H)-;

G is a member selected from the group consisting of:



J is a direct link;

Z-L is a member selected from the group consisting of:



5. A compound according to claim 1, of the formula:

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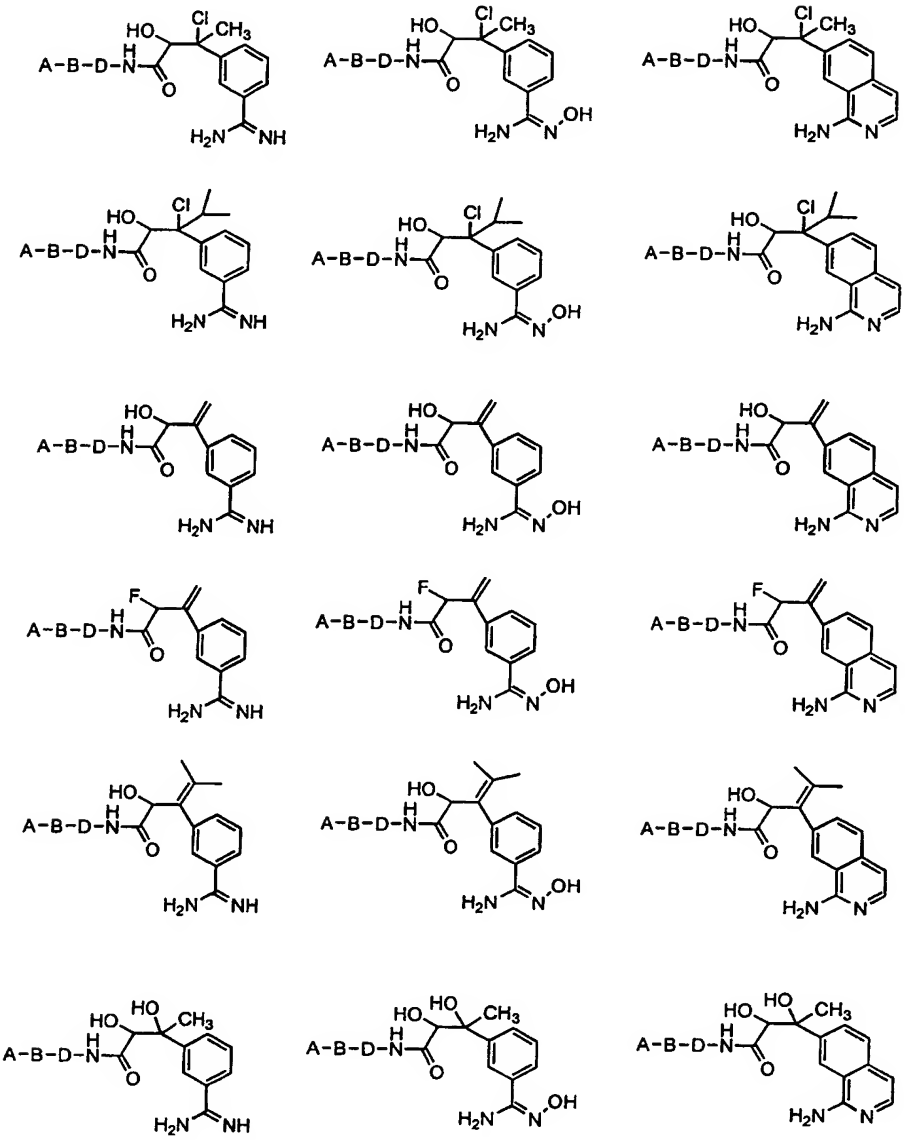
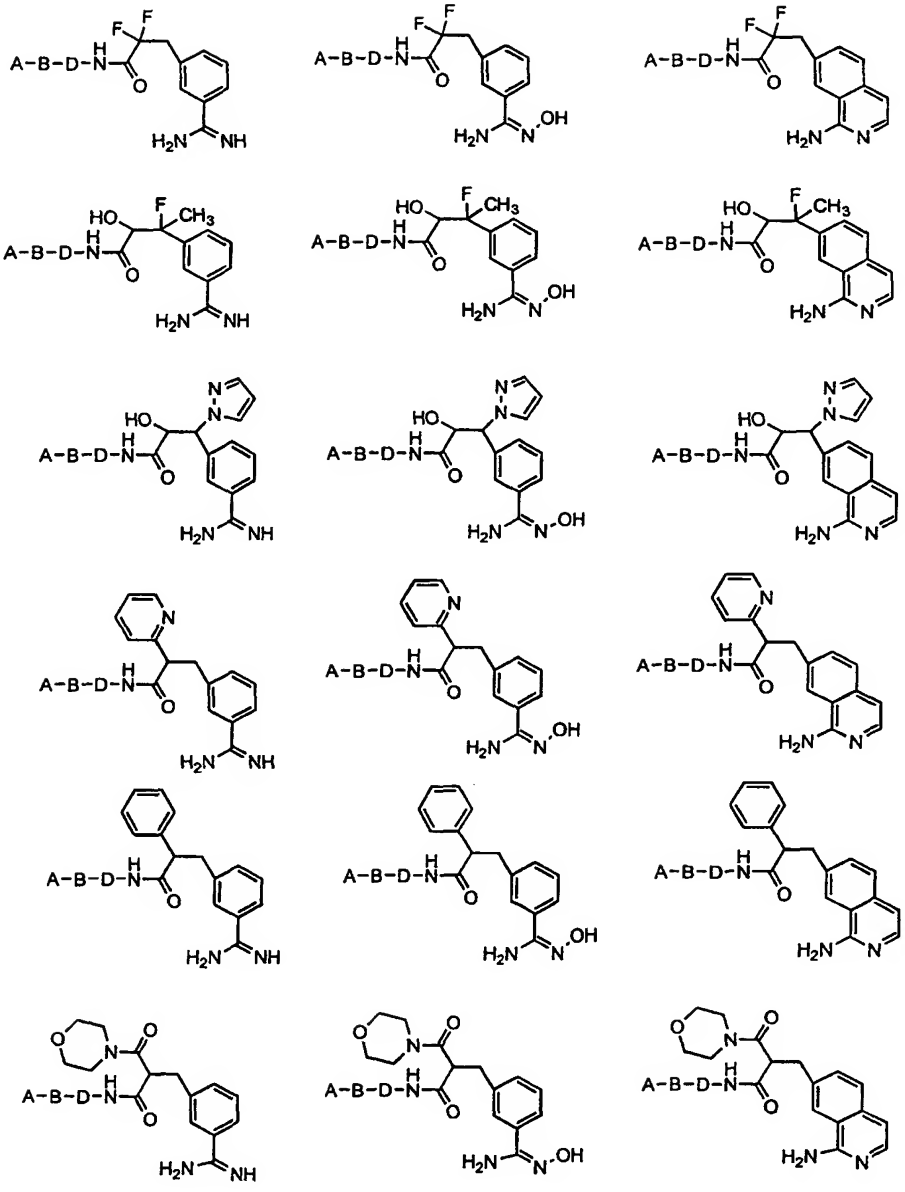
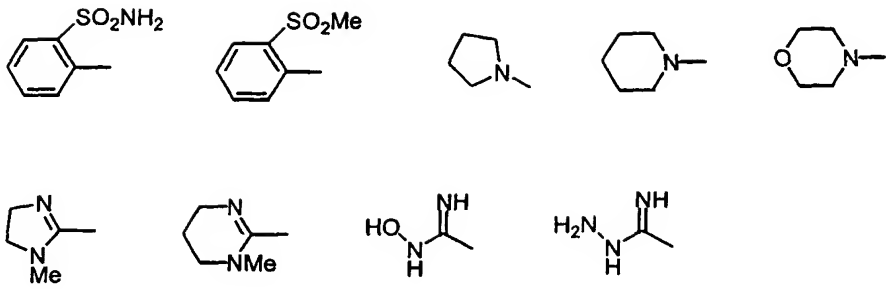




Wherein

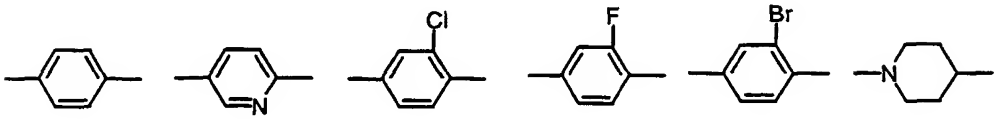
A is a member selected from the group consisting of:



Y is a member selected from the group consisting of:

a direct link, -C(=O)-; -N(-CH_3)-; -N(CH_3)-CH_2-; -C(=NH)-, -CH_2-, –C(=S)-, -NH-, and -SO_2-;

D is a member selected from the group consisting of:



6. A pharmaceutical composition for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising a pharmaceutically acceptable carrier and a compound of claim 1.

7. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising the step of administering to said mammal a therapeutically effective amount of a compound of claim 1.

8. The method of claim 7, wherein the condition is selected from the group consisting of: acute coronary syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-

thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation such as cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve, and conditions requiring the fitting of prosthetic devices.

9. A method for inhibiting the coagulation of biological samples, comprising the administration of a compound of claim 1.

INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/US 00/14207

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C311/46 A61K31/18 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 886 191 A (DUFFY DANIEL EMMETT ET AL) 23 March 1999 (1999-03-23) claim 6	1-9
X	WO 98 01428 A (DU PONT MERCK PHARMA) 15 January 1998 (1998-01-15) claims 6,10,12	1-9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 September 2000	02 [illegible] 00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Janus, S

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/14207

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 7-9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-9(in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-9(in part)

Present claims 1-5 relate to an extremely large number of possible compounds. The formula of claim 1 even includes simple compounds such as N-methyl-2-phenylacetamide. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed in the examples, namely those parts relating to the compounds of the formula given in claim 1 wherein A-Y-D-E- is 4-(2-aminosulfonylphenyl)phenylaminocarbonyl.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. .onal Application No
PCT/US 00/14207

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5886191 A	23-03-1999	US 6043257 A	28-03-2000
WO 9801428 A	15-01-1998	AU 3645697 A	02-02-1998
		CA 2259573 A	15-01-1998
		EP 0960102 A	01-12-1999